ENVIRONMENTAL TOBACCO SMOKE:
A COMPENDIUM OF TECHNICAL INFORMATION

May 1991 DRAFT

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PREFACE

This compendium of technical perspectives on Environmental Tobacco Smoke (ETS) is intended to be a useful resource document for a diverse audience, including: decision-makers such as labor and management officials concerned with workplace exposures, public health officials and corporate medical directors who are concerned with making health policy recommendations, educators, industrial hygienists and safety officers, ETS researchers, indoor air pollution investigators, and legislators who are considering legislation to restrict smoking in workplaces, restaurants, and public access buildings. Although the technical level varies, even the more technical treatments do not require a specialist's knowledge for understanding. There are eleven chapters in this compilation, including health effects of active smoking in adults and passive smoking in children and adults, ETS exposure and dosimetry, comfort aspects, ventilation and ETS, public beliefs about the harm of ETS and attitudes toward controls, and effective workplace smoking policies, each of which is aimed at a somewhat different audience. Although not all chapters will appeal equally to such a varied group, it is hoped that the technical information in this document, written by experts in the field, will provide information necessary to allow the public, corporations, government agencies, and legislators to make well-informed choices regarding exposure to ETS.

This perspective on ETS reflects the viewpoints and expertise of authors who were selected based upon their publications and recognition as experts on various aspects of ETS. Accordingly, the opinions expressed do not necessarily represent the official policies of the sponsoring agencies.

This document is the result of a coordinated effort jointly sponsored and produced by the Environmental Protection Agency (EPA) (chapters 2,3,4,6,7, and 8), the National Cancer Institute (NCI) (chapters 1,5), the Office on Smoking and Health (Centers for Disease Control) (chapter 9), the National Heart, Lung, and Blood Institute (chapter 10), and the Office of Disease Prevention and Health Promotion (Department of Health and Human Services) (chapter 11).

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INTRODUCTION

In 1986, the Surgeon General and the National Research Council, the latter under contract to EPA, examined the health effects of the breathing of Environmental Tobacco Smoke (ETS) by nonsmokers (also known as involuntary or passive smoking). They agreed that passive smoking caused lung cancer in nonsmoking adults, caused increased rates of respiratory infections in children, caused acute noxious effects in many nonsmokers, and was a major contributor to indoor air pollution. Subsequent to the publication of these documents, smoking restrictions began to proliferate. However, a number of diverse technical questions arose concerning public attitudes toward smoking restrictions, health and comfort effects, factors affecting exposure, measuring environmental concentrations of ETS, effects of ventilation on ETS and indoor air quality, nonsmokers' uptake of tobacco combustion products, and corporate experience in effective smoking policy, all comprise chapters in this compendium. In the interest of providing answers to this complex of questions, this technical compendium was commissioned. A brief summary of each chapter follows.

Chapter 1 demonstrates that high dose exposures to tobacco smoke, i.e., the effects of smoking on smokers, are very toxic, causing cancers, cardiovascular diseases, and respiratory diseases. It is graphically illustrated why cigarette smoking is now recognized as the Nation's single largest cause of premature death and disability.

Chapter 2 reviews studies of the concentrations of certain ETS constituents observed in homes, offices, and other locations by personal exposure monitors. It is concluded that ETS is the primary contaminant contributing to respirable particulate air pollution, and contributes substantially to other indoor contamininants such as benzene, carbon monoxide, and others. Even in low doses, tobacco smoke contains a wide variety of toxins, including many carcinogens.

Chapter 3 treats the methods of assessing nonsmoker's exposure to environmental tobacco smoke by atmospheric markers, and the measurement of these marker substances in indoor air. It is concluded that atmospheric monitoring for respirable particles or nicotine from ETS is critical for assessing exposures and control efforts, and that a number of reliable methods are available for such monitoring.

Chapter 4 provides a detailed treatment of the absorption and metabolism of tobacco combustion products by nonsmokers. It shows that absorption has been conclusively demonstrated by studies of nicotine and its metabolite, cotinine, in the body fuids of nonsmokers, and that such biomarkers represent a reliable specific method for assaying the level of uptake of ETS. This exemplifies

that low dose exposure to tobacco smoke leads to the absorption of toxins from the smoke in amounts sufficient to potentially cause disease.

Chapter 5 discusses the evidence that low dose exposure to tobacco smoke has been observed to increase the risk of lung cancer in nonsmokers, and discusses conclusions of the World Health Organization, the National Research Council, and the U.S. Surgeon General that ETS exposure increases lung cancer incidence in nonsmokers.

Chapter 6 discusses the evidence that low dose exposure to tobacco smoke has been observed to increase the risk of heart diseases in nonsmokers, and discusses the epidemiological, biochemical, and biological bases for this inference. It is concluded that the combined epidemiological and physiological evidence suggests that ETS exposure is a cause of heart disease in nonsmokers.

Chapter 7 investigates the assessment of nonsmokers' exposures to ETS by mathematical modeling, atmospheric indicators, and biomarkers in body fluids. Exposures assessed by these various methods produce consistent results. Because of the large source strength of tobacco-burning products, exposure to environmental tobacco smoke is inadequately controlled by measures short of physical separation of smokers and nonsmokers on different ventilation systems, making ETS a significant indoor pollutant of buildings.

Chapter 8 explores the effects of ventilation on the perception of odor and irritation from ETS in both nonsmokers and smokers, and shows that attempts to control the odor and irritation of ETS through ventilation and air cleaning have significant limitations.

Chapter 9 shows through national surveys of trends in public attitudes, that the general public, including both smokers and nonsmokers, believe that tobacco smoke polluted air is harmful and a large majority find it irritating. There is widespread support for restrictions against smoking, particularly in the workplace.

Chapter 10 discusses the evidence that smoking both at home and in daycare centers harms children and infants from tobacco-smoke polluted air. This has direct implications for public education of both parents and daycare providers, as well as for state policies and regulations affecting facilities which offer daycare.

Chapter 11 points out the common solution to the problem of ETS is source control, and examines features of corporate smoking policies in the workplace, with attention to benefits, incentives, employee and union involvement, and education. Case histories are

discussed involving several major corporations, detailing problems encountered and successes. It is concluded that smoke free workplaces have been achieved in a variety of settings. If thoughtfully implemented, they enjoy widespread support.

CHAPTER 1

EFFECTS OF SMOKING ON SMOKERS

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Cigarette smoking is the nation's leading cause of premature death and disability. In 1985, smoking caused approximately 390,000 deaths in the United States (Figure 1). By 1991, this number had increased to 440,000. In addition, tens of millions of people suffer from chronic disabling diseases and conditions caused or aggrevated by smoking. Every medical authority and organization who has objectively examined the evidence linking smoking to early death and disability has reached a similar conclusion. The evidence that smoking is a major health threat is staggering: over 50,000 citations from dozens of cultures are in the scientific literature. Smoking causes or is associated with cancers of the lung and bronchus, larynx, lip and oral cavity, bladder, pancreas, kidney, stomach and cervix, coronary artery disease, cerebrovascular disease (stroke), atherosclerotic aortic aneurysm, atherosclerotic peripheral vascular disease, chronic bronchitis, emphysema, low birth weight babies, and unsuccessful pregnancy. This chapter concentrates on the relationship between active smoking and three diseases caused by ETS -- lung cancer, heart disease, and nonmalignant lung disease. While there are qualitative differences between the mainstream smoke inhaled by the smoker and the ETS nonsmokers inhale, both forms of tobacco smoke contain the same carcinogens, irritants, and other toxins. The effects of high doses of smoke on smokers thus provide an indication of what effects low dose exposures of ETS would be expected to have on nonsmokers. This connection is particularly important because the diseases active smoking causes exhibit dose-response relationships, with higher doses producing greater effects. Because no threshold has been demonstrated for the carcinogenic and other effects of tobacco smoke on the body, the existence of a dose-response relationship suggests that ETS would provide similar, but smaller, dangers than active smoking.

Cancer

Most estimates in the scientific literature indicate that nearly one-third of all U.S. cancer deaths result from cigarette smoking. Of the approximately 136,000 cancer deaths which occurred in 1985 because of smoking, 106,000 are of the lung (Figure 1). Lung cancer alone is responsible for fully one-quarter of all

cancer mortality; were it not for the increasing number of deaths from lung cancer produced by smoking, we would be experiencing a substantial decline in the cancer death rate in the United States. Approximately 85 to 90 percent of all lung cancer deaths are smoking related. The evidence linking smoking and excess cancer mortality is so strong that only the tobacco lobby continues to claim that no causative role has been established. An examination of the association between cigarette smoking and lung cancer graphically illustrates smoking's role in the causation of neoplastic diseases.

Tobacco smoke contains at least 43 known or suspected human carcinogens (Table 1), several of which are regulated by the federal government as environmental toxins. There is no known threshold for the carcinogenic effects of these agents.

A host of epidemiological studies published during the last two decades provides an abundance of data which demonstrate that exposure to these carcinogens because of smoking leads to an increase in cancer deaths. In particular are the major prospective studies on smoking and health. These studies, conducted in the United States, Canada, England, Japan and Sweden represent some of the largest population based studies ever undertaken by medical science (Table 2). They involved enrolling healthy men and women into a study design and then followed these individual over time. Numerous factor about them were recorded including where they lived, their occupations, dietary habits, whether they used tobacco, access to health care, and many other factors. As a group, these eight studies in the United States, the U.S. Veteran's Study and the American Cancer Society (ACS) 25-state Study contained cohorts of 290,000 and 1 million persons respectively. The Veteran's Study continues to this day and this cohort has been followed prospectively for 26 years. These studies convincingly demonstrate that smoking causes cancer.

Lung Cancer

Lung cancer mortality rates are strongly influenced by the total dose of cigarette smoke received. If one smokes more cigarettes per day, inhales deeply, if they started smoking at an early age had has smoked for many years, the risk for lung cancer is increased dramatically.

The most often used measure to gauge lung cancer mortality is the number of cigarettes consumed daily. In the ACS 25-state study, for example, among males smoking less than 1/2 pack per day their lung cancer rate was nearly 5 times greater than that of a nonsmoker. With each increase in the number of cigarettes consumed daily, a corresponding increase in lung cancer mortality is observed (Figure 2). For those smokers consuming two or more packs daily, their lung cancer mortality is about 24 times greater than

that of the nonsmoker. At the other extreme, even light smokers, who consume only 1-9 cigarettes per day, see a quadrupling of the risk of lung cancer.

An inverse dose-response relationship exists between an early age of regular smoking and lung cancer mortality. In the U.S. Veterans Study, those smokers who started smoking in their early teens had substantially higher lung cancer death rates than those who started in their late teens or twenties (Figure 3). Those who began smoking before age 15 experienced a 19-fold greater lung cancer mortality, compared to a slightly greater than 5-fold excess risk for those who initiated their behavior after age 25.

These results demonstrate that a dose-response relationship exists for exposure to the carcinogens in cigarette smoke and the risk of death from lung cancer: the greater the lifetime exposure to tobacco smoke, the greater the risk.

Further evidence for the existence of a dose-response relationship comes from follow-up of people who stop smoking and so remove the exposure from the carcinogenic agents in mainstream smoke. When an individual stops smoking, his or her lung cancer risk declines relative to the continuing smoker. After about 15 years off cigarettes the former smoker's lung cancer risk approaches that of the life-long nonsmoker. However, it appears that some excess risk may be carried throughout life. This residual risk is strongly influenced by the individual's total lifetime exposure to the agent and the total number of years of smoking cessation.

The presence of a dose-response relationship between smoking and lung cancer, combined with the fact that there are significant elevations in risk associated with even the lowest levels of smoking, demonstrates that there is no threshold for the carcinogenic effects of cigarette smoke. This result from active smokers is consistent with the observed elevations of lung cancer risk among nonsmokers exposed to ETS.

Coronary Heart Disease

In contrast to cancer, in which smoking produces the disease through the cumulative effects of long term exposure to the carcinogens and co-carcinogens in the smoke, smoking effects the cardiovascular system immediately as well as over the long term.

The carbon monoxide in the smoke reduces the oxygen carrying capacity of the blood by binding to hemoglobin competitively with oxygen. Nicotine is a vasoconstrictor, which increases blood pressure and narrows coronary arteries. Smoking causes release of catecholamine, which increase blood pressure and heart rate. Smoking also increases platelet aggregation and adhesion, which contributes to the development of atherosclerosis. All these

effects occur immediately upon smoking and resolve relatively quickly after stopping smoking. As a result, one year after stopping smoking, the excess risk of death from heart disease falls by half; the same drop in risk for lung cancer takes 10 years. As with cancer, these effects exhibit a dose-response relationship, with greater more smoking and smoking in combination with other heart disease risk factors, increasing the risk of death from coronary heart disease. As with cancer, there is no threshold for these effects, so the effects of active smoking on the heart and cardiovascular system support the biological plausibility of the observed effects of ETS on the heart.

Coronary heart disease (CHD) continues to be this nation's leading cause of death, and for nearly 20 years, medical research has shown that smoking is one of the major independent risk factors or causes of CHD (along with high blood pressure and high cholesterol levels). In the final report of the Pooling Project, an interaction between smoking and other risk factors was observed (Figure 4). Each independent risk factor contributed about the same increased level of risk, however, when two or more factors were present, the risk of a major CHD event was increased beyond the sum of the independent risk -- thus, synergistic effect was created when two or more risk factors were present. Overall, smokers have a 70% greater CHD death rate, a two- to fourfold greater incidence of CHD, and a two- to fourfold greater risk for sudden death than nonsmokers.

Dose-response relationships between cigarette smoking and CHD mortality have been demonstrated for several measures of exposure to cigarettes, including the number of cigarettes smoked per day, the depth of inhalation, age at which smoking began, and the number of years of smoking. Smoking cigarettes with reduced yields of tar and nicotine does not reduce CHD risk, probably because these cigarettes do not have reduced yields of carbon monoxide and other combustion products which affect the cardiovascular system.

The independent risk of CHD for smoking is greater at the younger age groups although the greatest number of excess CHD deaths due to smoking actually occurs in the older age groups (Figure 5). Smoking has also been shown to increase the risk for other cardiovascular diseases, including peripheral vascular disease, cerebrovascular disease (at younger age groups), and aortic aneurysms. For women, smoking can interact with oral contraceptives to greatly increase the risk factor for fatal and nonfatal myocardial infarction and subarachnoid hemorrhage.

Smokers exhibit more atherosclerosis, both in the aorta and coronary arteries. Cigarette smokers who continue to smoke following transluminal coronary angioplasty appear more likely to require repeat angioplasty than nonsmokers, suggesting that the effects of smoking on atherosclerosis occur quickly. The polycyclic aromatic hydrocarbons which result from the combustion

of the smoking materials contribute to these effects. The increase in platelet adhesion observed in smokers also contributes to the development of atherosclerotic plaque.

Cigarette smoking aggravates the conditions of people with CHD. Smokers have a more difficult course following coronary artery bypass surgery. Smokers who experience angina pectoris have a higher risk of death than nonsmokers, a poorer prognosis following non-fatal myocardial infarction, and a greater risk of sudden death. Smoking increases the risk of silent ischemia in patients with stable angina.

Many public health estimates place the total number of excess cardiovascular disease (including stroke) deaths due to smoking to be greater than those due to cancer (Figure 1). Up to 30 percent of all CHD deaths may be due to cigarette smoking and its interaction with other risk factors.

These effects all exhibit a dose-response relationship with no threshold in active smokers, with detectable damage even among light smokers. These facts support the biological plausability of the evidence linking ETS with heart disease in nonsmokers.

Nonmalignant Respiratory Diseases

In addition to causing lung cancer, smoking causes or aggravates several related nonmalignant respiratory diseases, including emphysema, asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD). While the number of smoking-induced deaths classified due to chronic obstructive pulmonary disease (COPD) is smaller than for cancer or cardiovascular disease (Figure 1), COPD afflicts about 12 million Americans. Even if not fatal, COPD and related disorders such as emphysema severely debilitate the victim and represent a substantial number of people who become disabled due to their condition, unable to work or even seek employment.

For many years cigarette smoking has been known to increase the risk of developing and dying from COPD. Even the first Surgeon General's Report issued in 1964 identified a causative role between smoking and chronic bronchitis. As with lung cancer, the risk of contracting and dying from COPD is substantially elevated among smokers (Figure 6) and this risk increases with an increased dose of cigarette smoke received; as with the other smoking-induced diseases discussed in this chapter, there is a positive dose-response relationship. Mortality rations for COPD in smokers versus nonsmokers are very high, exceeding 30 to 1 for heavy smokers (Figure 7).

Smoking also has a dramatic effect on lung function. The normal rate of lung function decline with increasing age is accelerated in cigarette smokers (Figure 8). These effects

probably reflect damage to the small airways of the lungs as well as a thickening and increased reactivity of the airways in response to chronic exposure to the irritants in cigarette smoke. The volume an individual and exhale in one second of forced expiration (FEV_1) is a measure of small airway function. Figure 9 shows that FEV_1 falls in a dose-dependent manner as the amount of smoking increases. There is no safe level of exposure: there is a measurable decrement in pulmonary function even among light smokers.

Stopping smoking partially reverses the nonmalignant effects of the respiratory system (Figure 8). When one stops smoking, the decline in lung function with age resembles that of a nonsmoker, but a permanent decrement in lung function remains, indicating some permanent damage. The amount of this permanent deficit depends on the duration and intensity of smoking.

ETS exposure produces similar, but more modest nonmalignant pulmonary effects. FEV_1 is reduced in passive smokers among both children and adults to levels similar to that observed in light smokers. Children of parents who smoke develop more asthma, bronchitis and other respiratory problems. The rate of lung development in children exposed to ETS is smaller than that of unexposed children. These effects of ETS are what one would expect based on the effects of active smoking.

Conclusions

This chapter has reviewed the effects of active smoking in on those cancers, heart disease, and nonmalignant pulmonary diseases which have also been identified with passive smoking. In each case, cigarette smoking significantly increased the risk of disease in smokers in a dose-dependent manner. There is no evidence of a threshold level for adverse effects. Because ETS is similar to (but more toxic than) mainstream smoke, these effects on the smoker help provide evidence for the biological plausibility for the epidemiological evidence linking ETS with lung cancer, heart disease, and nonmalignant respiratory disorders, after accounting for the lower dose the involuntary smoker receives.

1. There is a dose-response relationship between exposure to tobacco smoke and the diseases of smoking.

2. There are no discernable thresholds of exposure for the diseases of smoking.

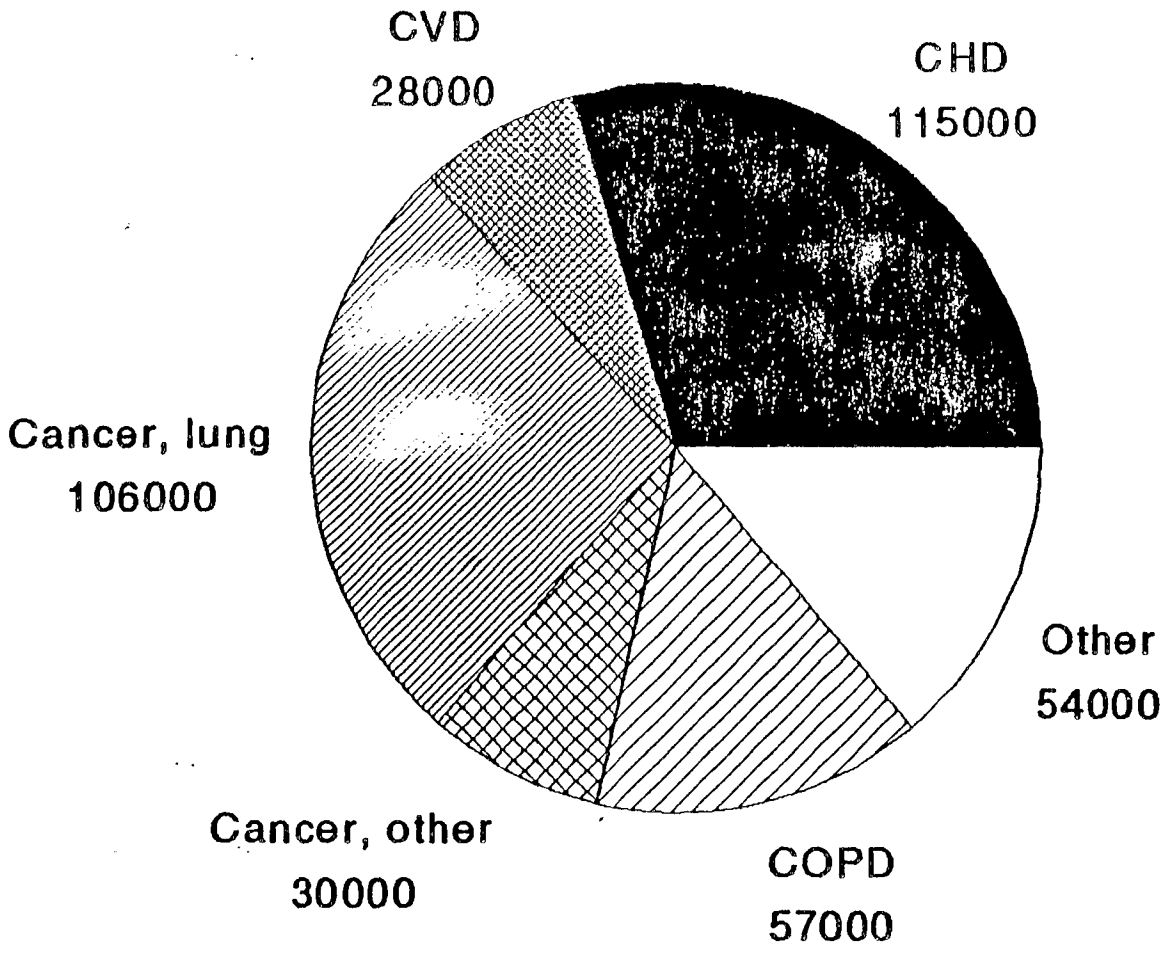
3. Adverse health effects observed in smokers provide biological plausibility for the occurrence of those diseases in nonsmokers.

TABLES AND FIGURES, CHAPTER 1

FIGURE 1.

US Deaths Attributed to Smoking in 1985

Source: US Surgeon General, 1989



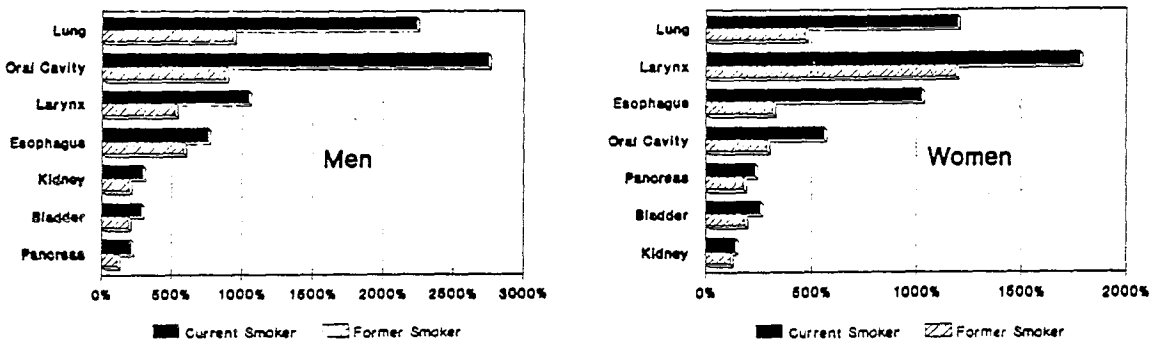


FIGURE 2 • Percent increased cancer morality risk, by site and gender, in current and former smokers as derived from the American Cancer Society 50-State Study.

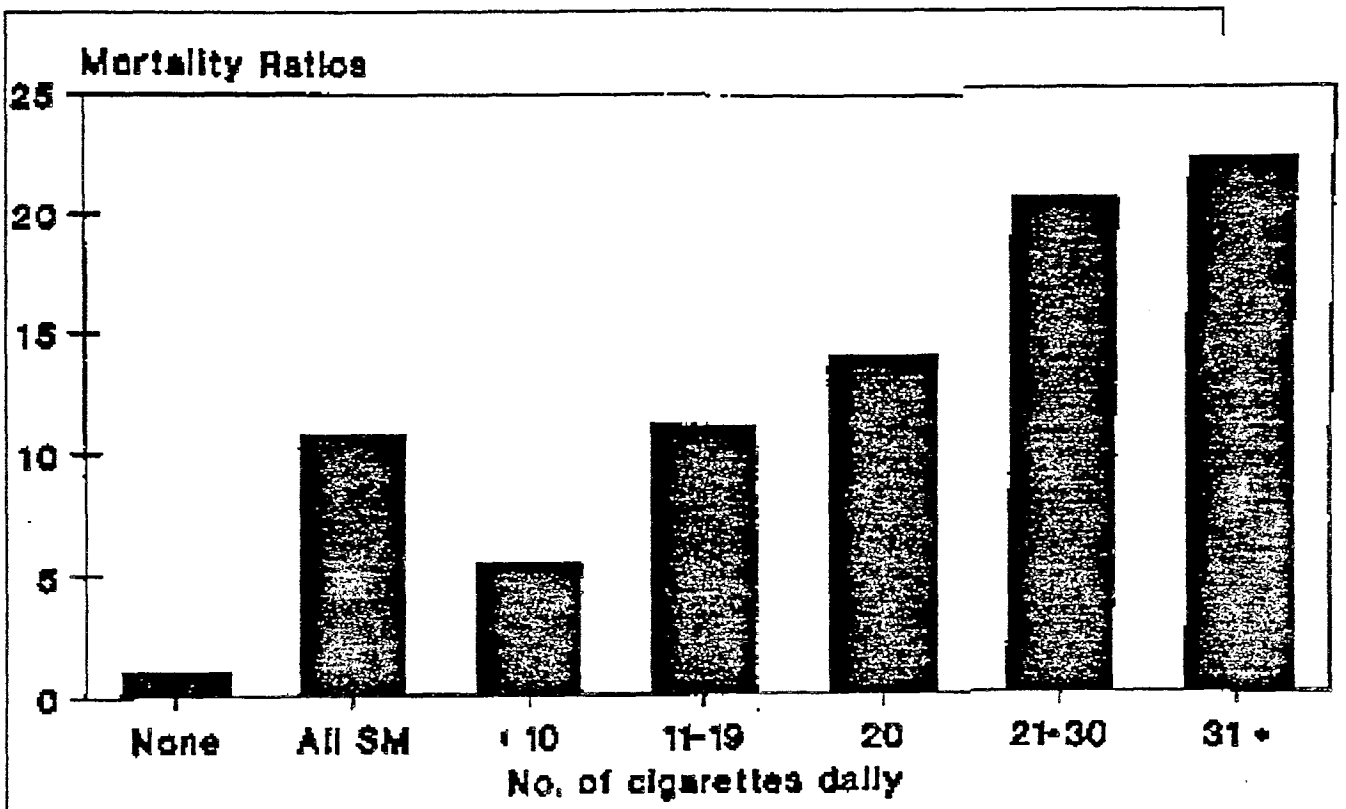


FIGURE 3.

(1989 SURGEON GENERAL'S REPORT, p. 49)

FIGURE 4.

Lung cancer mortality ratios for males, by age began smoking — U.S. Veterans' Study

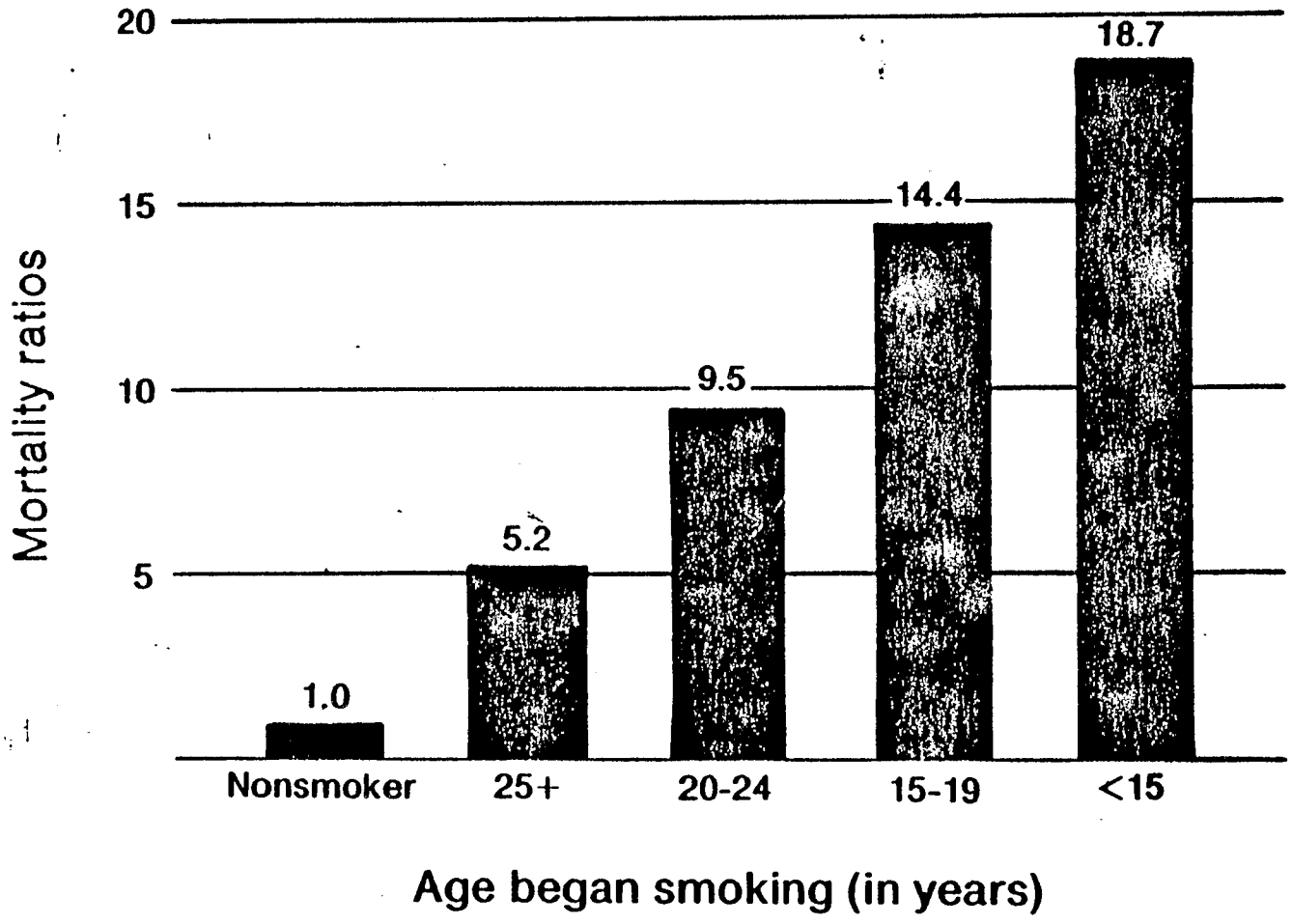
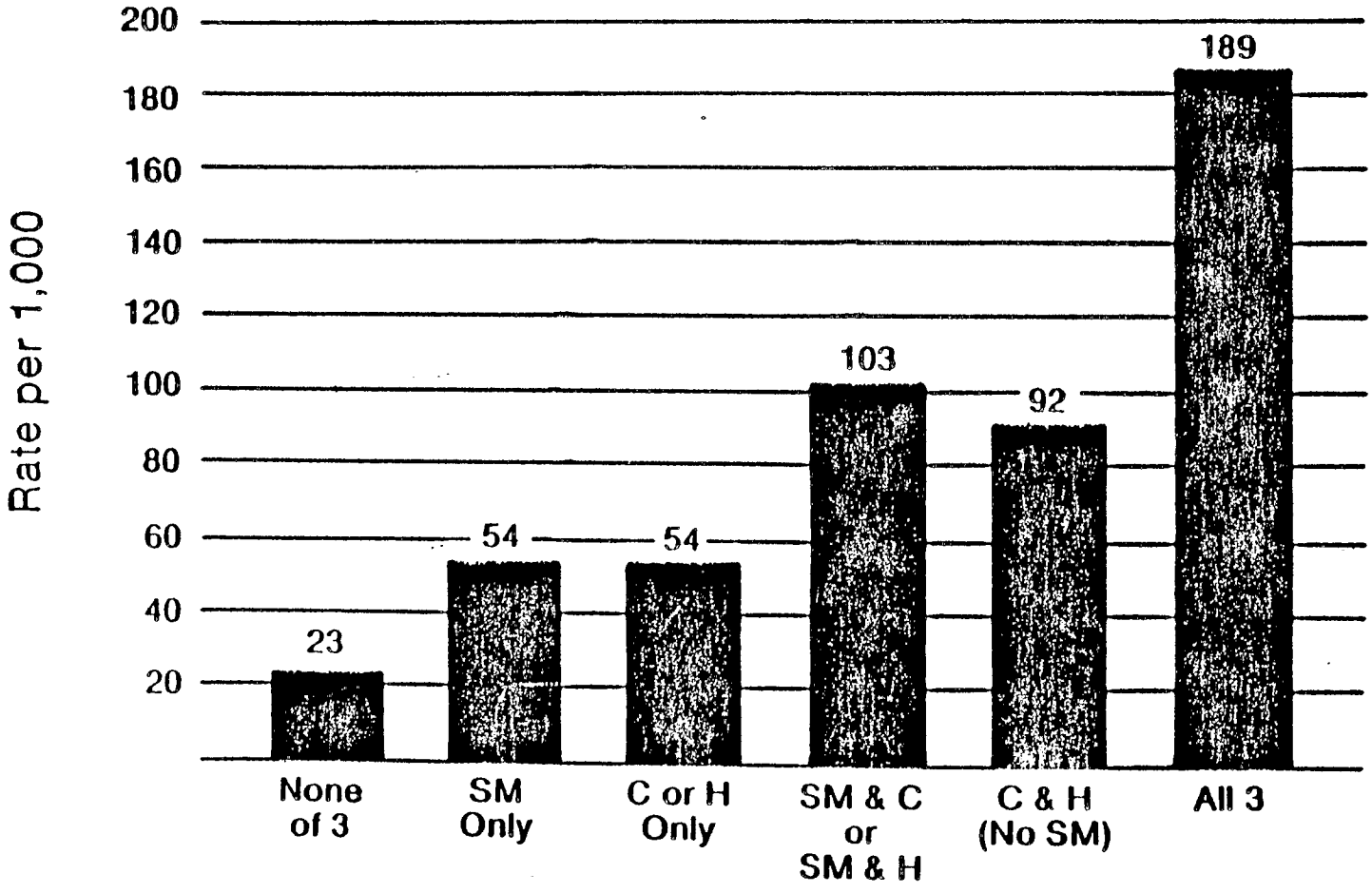


FIGURE 5.

Major risk factor combinations, 10-year incidence of first major coronary events, men age 30-59 at entry, Pooling project



SM = smoker, C = cholesterol, H = hypertension

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Coronary heart disease deaths, smokers vs. nonsmokers

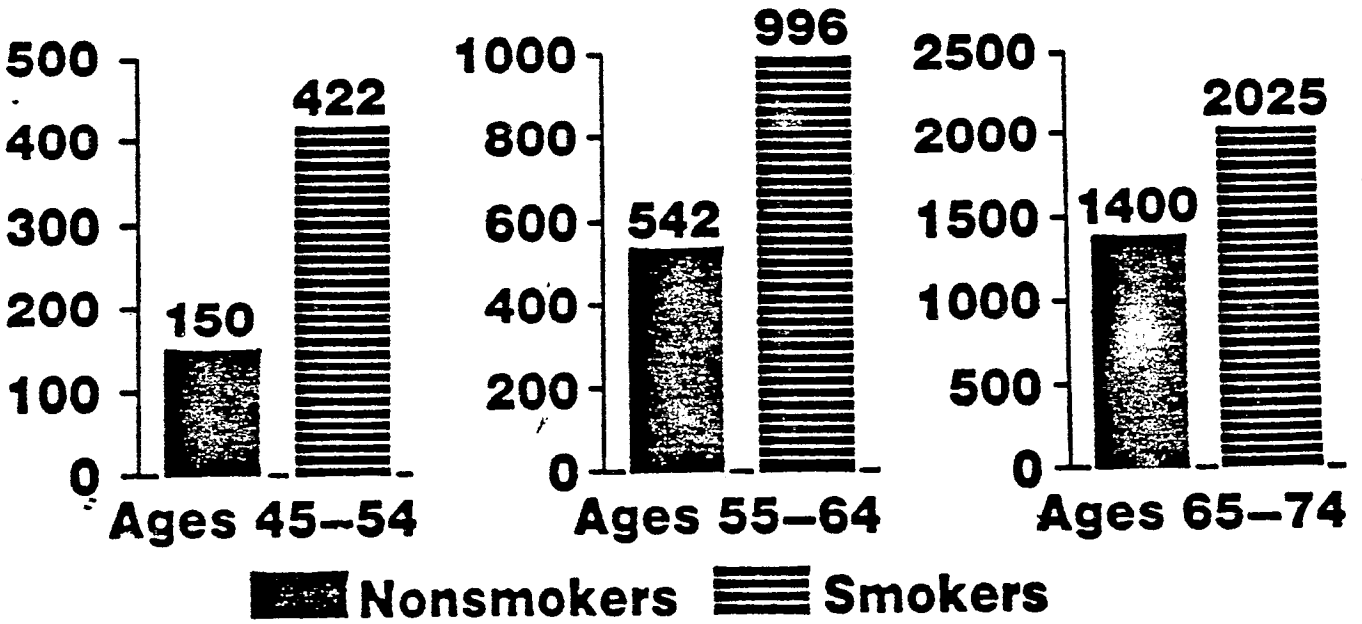


FIGURE 6.

COLD deaths smokers vs. nonsmokers

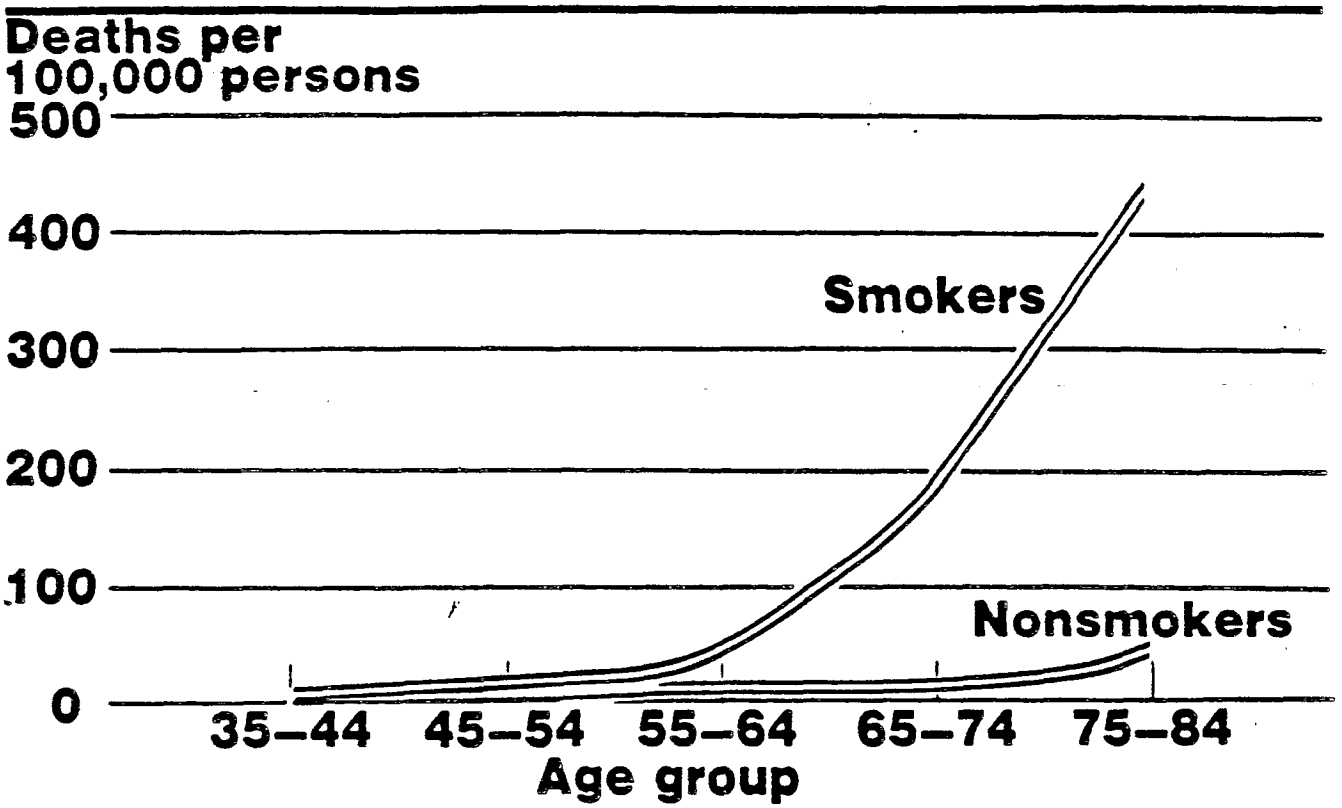
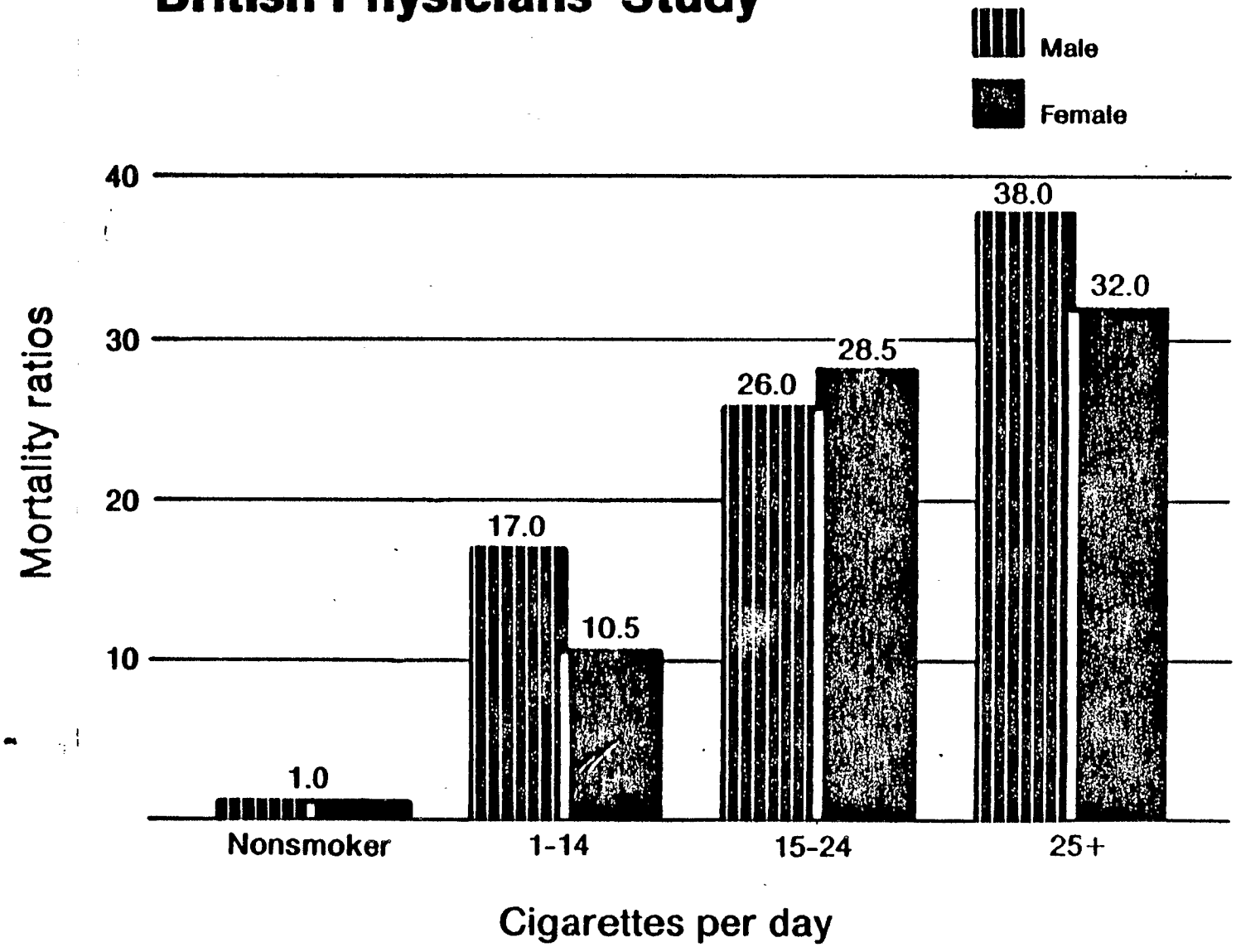


FIGURE 7.

FIGURE 8.

COLD mortality ratios for men and women, by number of cigarettes smoked per day, British Physicians' Study



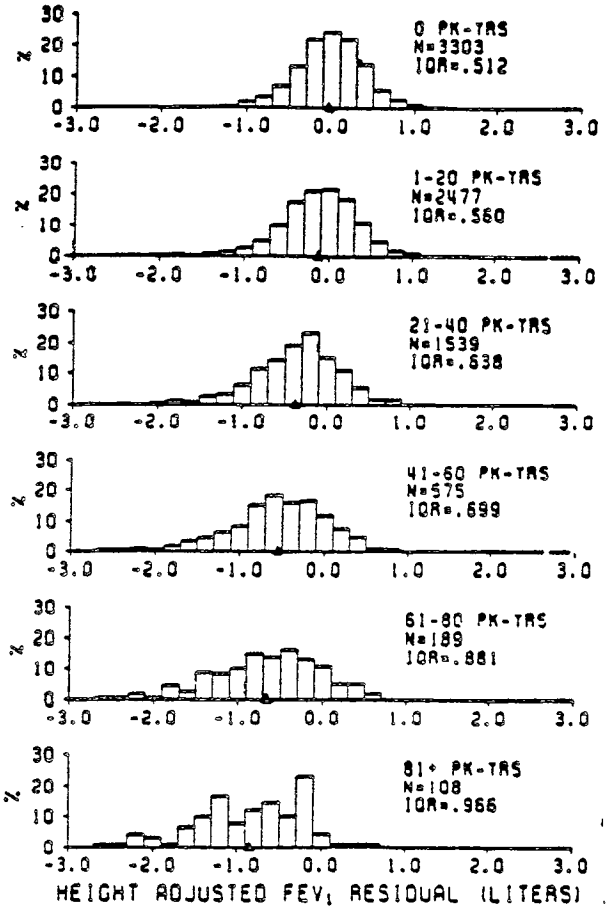


FIGURE 10. —Percent distribution of predicted values of forced expiratory volume in 1-sec (FEV_1) in subjects with varying pack–years of smoking.

NOTE: Triangle indicates mean. IQR is interquartile range.

SOURCE: Burrows et al. (1977); Dockery et al. (1988).

TABLE 1. Expected Cancer Deaths Caused by Smoking—United States 1989

Site	1989 Cancer Deaths Expected	Smoking Attributable Risk (%)	Estimated Deaths Due to Smoking
Men			
Buccal cavity and pharynx	5,775	92	5,313
Larynx	3,000	81	2,430
Lung	93,000	90	83,700
Esophagus	6,900	78	5,382
Bladder	6,900	47	3,243
Kidney	6,000	48	2,880
Pancreas	12,500	29	3,625
Total			106,573
Women			
Buccal cavity and pharynx	2,875	61	1,754
Larynx	700	87	609
Lung	49,000	79	38,710
Esophagus	2,500	75	1,875
Bladder	3,300	37	1,221
Kidney	4,000	12	480
Pancreas	12,500	34	4,250
Total			48,899
Total men and women expected to die of cancer in 1989			502,000
Percent attributed to smoking			.31
Total excess cancer deaths due to smoking expected in 1989			155,472

TABLE 2. (SG, 1989: p. 86-87)

—Tumorigenic agents in tobacco and tobacco smoke

Compounds	Processed tobacco (per gram)	Mainstream smoke (per cigarette)	Evidence for IARC evaluation of carcinogenicity	
			In lab animals	In humans
Aromatic amines				
2-Toluidine		30–200 ng	Sufficient	Inadequate
2-Naphthylamine		1–22 ng	Sufficient	Sufficient
4-Aminobiphenyl		2–5 ng	Sufficient	Sufficient
Aldehydes				
Formaldehyde[a]	1.6–7.4 µg	70–100 µg[a]	Sufficient	NA
Acetaldehyde[a]	1.4–7.4 mg	18–1,400 mg[a]	Sufficient	NA
Crotonaldehyde	0.2–2.4 µg	10–20 µg	NA	NA
Miscellaneous organic compounds				
Benzene		12–48 µg	Sufficient	Sufficient
Acrylonitrile		3.2–15 µg	Sufficient	Limited
1, 1-Dimethylhydrazine	60–147 µg		Sufficient	NA
2-Nitropropane		0.73–1.21 µg	Sufficient	NA
Ethylcarbamate	310–375 ng	20–38 ng	Sufficient	NA
Vinyl chloride		1–16 ng	Sufficient	Sufficient
Inorganic compounds				
Hydrazine	14–51 ng	24–43 ng	Sufficient	Inadequate
Arsenic	500–900 ng	40–120 ng	Inadequate	Sufficient
Nickel	2,000–6,000 ng	0–600 ng	Sufficient	Limited
Chromium	1,000–2,000 ng	4–70 ng	Sufficient	Sufficient
Cadmium	1,300–1,600 ng	41–62 ng	Sufficient	Limited
Lead	8–10 µg		Sufficient	Inadequate
Polonium-210	0.2–1.2 pCi	0.03–1.0 pCi	NA	NA
PAH				
Benz(a)anthracene		20–70 ng	Sufficient	NA
Benzo(b)fluoranthene		4–22 ng	Sufficient	NA
Benzo(j)fluoranthene		6–21 ng	Sufficient	NA
Benzo(k)fluoranthene		6–12 ng	Sufficient	NA
Benzo(a)pyrene	0.1–90 ng	20–40 ng	Sufficient	Probable
Chrysene		40–60 ng	Sufficient	NA
Dibenz(a,h)anthracene		4 ng	Sufficient	NA
Dibenzo(a,i)pyrene		1.7–3.2 ng	Sufficient	NA
Dibenzo(a,l)pyrene		Present	Sufficient	NA
Indeno(1,2,3-c,d)pyrene		4–20 ng	Sufficient	NA
5-Methylchrysene		0.6 ng	Sufficient	NA
Aza-arenes				
Quinoline		1–2 µg	NA	NA
Dibenz(a,h)acridine		0.1 ng	Sufficient	NA
Dibenz(a,j)acridine		3–10 ng	Sufficient	NA
7H-Dibenzo(c,g)carbazole		0.7 ng	Sufficient	NA
N-Nitrosamines				
N-Nitrosodimethylamine	ND–215 ng	0.1–180 ng	Sufficient	NA
N-Nitrosoethyl methylamine		3–13 ng	Sufficient	NA
N-Nitrosodiethylamine		ND–25 ng	Sufficient	NA
N-Nitrosopyrrolidine	ND–360 ng	1.5–110 ng	Sufficient	NA
N-Nitrosodiethanolamine	ND–6,900 ng	ND–36 ng	Sufficient	NA
N'-Nitrosonornicotine	0.3–89 µg	0.12–3.7 µg	Sufficient	NA
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	0.2–7 µg	0.08–0.77 µg	Sufficient	NA
N'-Nitrosoanabasine	0.01–1.9 µg	0.14–4.6 µg	Limited	NA
N-Nitrosomorpholine	ND–690 ng		Sufficient	NA

NOTE: ND, no data; NA, evaluation has not been done by IARC.

[a]The Fourth Report of the Independent Scientific Committee on "Smoking and Health" (1988) published values for the 14 leading U.K. cigarettes in 1986 (51.4 percent of the market) of 20–105 µg/cigarette (mean, 59 µg) for formaldehyde and 550–1,150 µg/cigarette (mean, 910 µg) for acetaldehyde

SOURCE: Hoffmann and Hecht, in press

TABLE 3.

Outline of Eight Major Prospective Studies

Authors	Doll Hill Peto Pike	Hammond	Dorn Kahn Rogot	Hirayama	Best Josie Walker	Hammond Horn	Weir Dunn Linden Breslow	Cederlof Friberg Hrubec Lorich
Subjects	British doctors	Males and females in 25 States	U.S. veterans	Total population of 29 health districts in Japan	Canadian pensioners	White males in nine states	California males in various occupations	Probability sample of the Swedish population
Population size Females	40,000 6,000	1,000,000 562,671	290,000 < 1%	265,000 142,857	92,000 14,000	187,000	68,000	55,000 27,700
Age Range	20-85+	35-84	35-84	40 and up	30-90	50-69	33-64	18-69
Year of enrollment	1951	1960	1954 1957	1966	1955	1962	1954	1963
Years of followup reported	20-22 years	12 years	16 years	13 years	6 years	4 years	6-8 years	10 years
Number of deaths	11,166	150,000	107,500	39,100	11,000	12,000	4,700	4,500
Person years of experience	800,000	8,000,000	3,500,000	3,000,000	500,000	670,000	480,000	550,000

TABLE 4 • Mortality Ratios for Men and Women 35 Years and Older According to Smoking Status at Time of Enrollment

	25-State Study		50-State Study	
	Current Smoker	Former Smoker	Current Smoker	Former Smoker
Men				
Lung	11.35	4.96	22.36	9.36
Oral	6.33	2.73	27.48	8.80
Esophagus	3.62	1.28	7.60	5.83
Larynx	10.00	8.60	10.48	5.24
Bladder	2.90	1.75	2.86	1.90
Pancreas	2.34	1.30	2.14	1.12
Kidney	1.84	1.79	2.95	1.95
Women				
Lung	2.69	2.59	11.94	4.96
Oral	1.96	1.89	5.59	2.88
Esophagus	1.94	2.15	10.25	3.16
Larynx	3.81	3.10	17.78	11.88
Bladder	2.87	2.31	2.58	1.85
Pancreas	1.39	1.38	2.33	1.78
Kidney	1.43	1.47	1.41	1.16
Uterus	1.18	—	—	—

Data from the Surgeon General's Report, 1989.[5]

CHAPTER 2

EXPOSURES TO INDOOR PARTICULATE AIR POLLUTANTS

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Throughout our lives, we are exposed to gaseous and particulate contaminants in the air. For some airborne contaminants, our exposure is dominated by their occurrence in outdoor air and the time we spend outdoors. However, even for the pollutants that have only outdoor sources, the air that ventilates our homes, offices, and vehicles originate outdoors. Considering chronic exposure or protection from acute episodic outdoor pollution events, the time we spend indoors and the protection these indoor environments provide are important considerations.

In the presence of indoor sources of contaminants such as unvented combustion, evaporation of solvents, and dispersion of microbiological organisms among others, the time-activity patterns of people in their use of these indoor environments become important considerations in determining exposures. People can have very different exposures to indoor contaminants depending on social, demographic and economic differences in the population, as well as the physical differences that exist across indoor environments. These differences are characterized by the use of the structure, its volume air flow and air exchange, the efficiency of contaminant removal and, most importantly, the generation rate of the source itself.

Thus, concentrations of air pollutants can and do vary depending on location. Outdoor pollutant levels may differ from indoor levels. Different indoor locations like homes, schools or workplace can also register varying pollutant levels. An individual's total exposure to air pollutants therefore depends on the time spent in each of these microenvironments and the various concentrations of air pollutants.

Time-Activity Patterns

The activity patterns of people determine the duration of exposure and, at times, the intensity of exposure to airborne

contaminants. The amount of time a person spends in different microenvironments is influenced by age, sex, occupation, social class, and season. Letz et al. (1984) studied the time-activity patterns of 332 residents of Roane County, Tennessee. The results of study showed that these individuals spent 75% of their time in the home. This figure was higher (84.9%) for housewives, unemployed and retired persons. Overall 10.8% of the participants time was spent at "work". Full-time employed individuals worked between 21-24% of the time. Of the remaining time, 8.5% was spent in public places, 9% in travel, and 2.8% in various other locations.

Quakenboss et al. (1982) studied the time allocation for 66 family members from 19 homes in Portage, WI. Individuals were put into one of five general subgroups which are shown in Table 1. Despite wide variations, each group spent most of the time at home. For all participants, total time spent indoors was 85%.

More recently, Quakenboss and his colleagues analyzed time-activity data for over 300 individuals in the Portage, WI area. Participants were categorized into three groups: workers, nonworkers, and students. Activity data was collected from both summer and winter seasons and is summarized in Table 2. Again all groups spent the largest percentage of their time in the home. Time spent outdoors decreased from summer to winter.

Infants, because they are essentially immobile, spend most of their time in the bedroom according to a recent study by Harlos et al. (1987). The rest of their time is usually spent in the living room, kitchen, or in travel as illustrated in Figure 1.

Knowing an individual's or a population's activity patterns is not sufficient in itself to determine exposure to contaminants. Outdoor pollutants do penetrate indoors and can undergo reactions. Indoor contaminant concentrations vary according to the source rate, air exchange and air flow, and reactions. Characterizing sources indoors will not always lead to accurate estimates of concentrations or exposures. Therefore, depending on the distribution of sources indoors and the degree of mixing, there may be considerable differences in pollutant concentrations across indoor environments.

Lebret (1985) examined the respirable suspended particulate (RSP) levels in rooms while participants were smoking or within one-half hour of smoking. He found significant variation between the living room kitchen and bedroom. Ju and Spengler (1981), who studied 24-hour average concentrations of respirable particulates, also found statistically significant variation between some rooms although the absolute differences were relatively small.

Monitoring

There are a number of different instruments available to monitor air pollutants. Often the type of instrument used depends on the exposure of interest. Immediate exposures are most important when studying irritant and acute allergic responses. For this type of exposure, instruments which take short-term or instantaneous readings are often used: the piezobalance or nephelometer are both used to measure particulates, the ecolyzer is used to measure carbon monoxide. One advantage to these types of instruments is their ability to detect peak pollutant levels.

For acute effects such as upper or lower respiratory infections, the exposures of interest range from hours to days. For increased prevalence of even a lifetime.(?) To measure these exposures, integrated or time-averaging methods are used. These methods include filters which are used to collect particles over long time periods.

EXPOSURE TO AIRBORNE PARTICLES

Size Distribution and Composition of Particulates

The distribution of particulates is essentially trimodal with peak diameters at approximately 0.02 μm, 0.5 μm and 10 μm as shown in Figure 2. These size modes reflect the origins of the particles and the physical chemical processes affecting them. The ultrafine fractions are typically fresh combustion emissions of aiken nuclei and condensing vapors. The submicron size (0.1-1 μm) has been called the accumulation mode. Again, incomplete combustion adds particles to this size range; however, the oxidation of gases such as SO_2 and NO_2 to form sulfates and nitrates are predominantly found in this range.

Particles larger than 1 μm can be of biological origin--fiber fragments, spores, pollens, and bacteria. Bursting bubbles and sea spray can generate condensation nuclei. But it is mostly abrasion and/or erosion that generate larger particles.

The fine particle fraction, or <2.5 μm, is produced by combustion or condensation of vapors. At least 75% of the sulfur, zinc, bromide and lead are found in this size range (Dzubay and Stevens, 1975). Particles <2.5 μm are very important for health reasons since these particles can reach the alveolar regions of the lungs.

Particles greater than 2.5 μm in diameter, or coarse particles, are usually formed by mechanical processes like grinding, crushing, and abrasion. At least 75% of the silicon, calcium and iron, elements commonly found in soil, appear in this size fraction (Dzubay and Stevens, 1975). Particles from 2.5-10 μm can be inhaled and can become deposited in the tracheobronchial

regions.

Environmental Tobacco Smoke

Environmental tobacco smoke (ETS) is a mixture of exhaled mainstream smoke and sidestream smoke. Sidestream smoke is the smoke that is formed by smoldering between puffs of a tobacco product and is the major source of ETS. Approximately half the tobacco in a cigarette is burned in the sidestream mode. The complex mixture that the smoker inhales with each puff of a cigarette, cigar, or pipe is called mainstream smoke. The portion of mainstream smoke that the smoker exhales and the small amount of vapor diffusing through the wrapping of the cigar or cigarette add little to ETS.

ETS consists of fresh and aged sidestream and mainstream smoke. The particle sizes which make up ETS vary due to coagulation (the process where two or more particles collide and combine to form a larger particle), evaporation, and the adhesion of particles to surfaces. The size distribution of particles is also affected by air dilution, relative humidity and temperature.

Under controlled conditions, several researchers have measured the particle size distribution of sidestream smoke (Keith and Derrick, 1960; Porstendorfer and Schraub, 1972; Hiller et al., 1982; Leaderer et al., 1984; Ingebrethsen and Sears, 1986). Based on these studies, the mass median diameter of sidestream smoke can be estimated to be between 0.2 μm and 0.4 μm. The mass median diameter is the diameter which divides the mass distribution in half, i.e. one half of the mass is contributed by particles larger than this diameter and one half by particles smaller. Because much of the time the tobacco is burning at substoichiometric conditions, particles are produced in the accumulation size mode. As ETS ages, the processes of coagulation cause particles to grow. This offsets mass loss due to evaporation.

Composition of ETS

Environmental tobacco smoke is made up of several thousand different chemical compounds. These compounds may be in the gaseous or solid phase or both. The chemical composition of sidestream smoke differs from that of mainstream smoke. Over 2,000 compounds have been measured in sidestream and mainstream smoke. Some of the constituents in the mainstream smoke of nonfilter cigarettes are listed in Table 3. Also given are ratios of these substances in sidestream smoke compared to mainstream smoke. A ratio of greater than 1.0 means the constituent is found in higher concentrations in sidestream smoke than mainstream smoke. Nicotine, a substantial component of tobacco combustion, is produced mainly in the particulate phase. However, as the ETS mixture dilutes and ages, the nicotine rapidly shifts to vapor phase. Chamber studies by McCarthy (1987) and others have

demonstrated that the half-life decay of nicotine is more than twice that of the particulate phase. A number of the constituents listed are carcinogens or suspected carcinogens according to the International Agency for Research on Cancer (IARC).

Measurement of ETS

The large number of constituents in ETS make it impossible to assess overall exposure based on measurement of each one. Instead most researchers have measured one or more compounds and have used those to estimate the total exposure to ETS. Changes in ETS composition over time and exposure conditions limit the accuracy of this method.

This chapter will discuss in detail only a few of the possible measures of ETS: particles, nicotine, cadmium and nitrosamine. Most of the data presented will be from studies involving cigarette smoke since this is a major source of indoor ETS. Little work has been done on pipe or cigar smoke.

Exposures to Environmental Tobacco Smoke

According to the U.S. Department of Commerce (1985) about 30% of adults in the U.S. are smokers. 40% of homes nationwide have at least one smoker. In a survey of over 10,000 children in six U.S. cities, the percentage of children living with one or more smoking adults varied from a low of 60% to a high of 75% (Ferris et al., 1979). Lebowitz and Burrows (1976) reported 54% of children in a study in Tucson had at least one smoker in the home. These data indicate that the potential for exposure to ETS in the home is greater than that inferred from national statistics. In part, this reflects the demographics of smoking where it is adults in their child-raising years that are more likely to be smokers than the overall average. Surveying a new cohort of elementary-age children in six U.S. cities reveals that on average, parental smoking has decreased between 10% to 15% over a decade (mid 1970's to mid 1980's).

Smoking between different demographic groups can vary widely and this will modify the exposure of nonsmokers to ETS. Overall, ETS exposure will depend on the proximity of an individual to the source of smoke. Patterns of smoking will be influenced by time, location, and type of activity.

MICROENVIRONMENTAL MEASUREMENTS OF CONCENTRATIONS

Concentrations of Particles and ETS

Numerous studies have been conducted using respirable suspended particulates (RSP) as markers for ETS. Both continuous and integrated measurements methods have been used. Although RSP

is not specific for the presence of smokers in the home and other indoor locations, the number of cigarettes smoked have shown to correlate well with RSP.

Particulate Concentrations in Homes

Spengler et al. (1981) measured 24-hour respirable particulate levels in 55 homes in six U.S. Cities. The mean monthly concentration across cities is presented in Figure 3, with indoor particulate levels similar to the outdoor levels. Table 4 shows the respirable particulate levels in the homes as a function of the number of smokers. The actual amount of smoking in the home was not reported. The researchers concluded that the major source of indoor particulates in smoking homes was cigarette smoke. Each smoker in the home raised the mean respirable particulate level by 20 $\mu g/m^3$.

Further analysis of the data by Dockery and Spengler (1981) showed that each cigarette smoked in the home increased the mean respirable particulate levels by 0.88 $\mu g/m^3$. In air conditioned homes, the respirable particulate levels increased by 2.11 $\mu g/m^3$ per cigarette per day. This increase was probably caused by recirculation of indoor air which reduced the cigarette smoke dilution.

More recently Spengler and colleagues (1986) analyzed RSP data from over 200 homes in Watertown, MA. Homes with smokers had RSP concentrations of 30 to 35 $\mu g/m^3$ higher than nonsmoking homes. RSP concentration and the number of cigarettes smoked per week were highly correlated. Models based on this data predict a contribution of 0.77 $\mu g/m^3$ per cigarette per day. This would mean a pack of cigarettes would increase the indoor RSP concentration by 15.5 $\mu g/m^3$.

Particulate Concentration in Offices

Using a piezobalance, Weber and Fischer (1980) monitored 44 workrooms at seven different companies in Switzerland. The workrooms had varying levels of smoking. A number of samples were taken in each room over a two-day period. After subtracting the particulate levels found in an unoccupied room, the mean particulate level for the 492 samples taken was 133 $\mu g/m^3$ with a standard deviation of 130 $\mu g/m^3$. The maximum concentration measured was 962 $\mu g/m^3$.

Quant et al. (1982) used a piezobalance to monitor three offices. The offices were divided into cubicles with half-wall partitions and contained both smoking and nonsmoking areas. Offices were monitored continuously for one work week. Figure 4 shows the results of continuous monitoring in one of the offices. For the three offices, the ten-hour day averages ranged from 37$\mu g/m^3$ to 89 $\mu g/m^3$.

Miesner et al. (1988) used both continuous and integrated methods to monitor in five office buildings in metropolitan Boston. Both filters and nephelometer were used to measure in 12 offices, one conference room, and a designated smoking room of a large nonsmoking office. In offices without smoking, concentrations typically ranged from 15 to 10 $\mu g/m^3$. In offices with smoking, concentrations were higher, ranging from 20 to 80 $\mu g/m^3$. In designated smoking areas, concentrations were 100 to 500 $\mu g/m^3$. Short-term concentrations measured with the portable MINIRAM exceeded 1000 $\mu g/m^3$ in one of the designated smoking areas.

Particulate Concentration in Offices

Repace and Lowry (1980) measured particulate levels in various indoor public facilities both in the absence and presence of smoking. For nonsmoking locations such as restaurants, libraries, a church, and a bakery, the mean indoor RSP level was less than 60 $\mu g/m^3$. Measurements taken in public facilities in the presence of smoking are shown on Table 5. Measurements range from 86$\mu g/m^3$ to 187 $\mu g/m^3$ for restaurants and cafes that permit smoking. Other areas where there are likely to be more smokers per area than in restaurants had much higher concentrations of particulate matter, ranging from 200 to 700 $\mu g/m^3$.

Besides monitoring in offices, Miesner et al. (1988) also took continuous and integrated RSP measurements in numerous public facilities including a library, museum, school, subway, bars, and restaurants. They found that for most public buildings where no smoking was present the particulate levels were low usually less than 30 $\mu g/m^3$. Levels in transportation facilities such as the subway and bus stations were slightly higher with a mean integrated measurement of 63 $\mu g/m^3$. Higher concentrations were found in smoking areas such as bars, restaurants and a public smoking room with a mean integrated measurement of 79 $\mu g/m^3$ and a standard deviation of 44 $\mu g/m^3$.

Concentration of Other Components of ETS

Numerous researchers have looked at other tracers for ETS. Because of its high specificity for tobacco smoke and its presence in high concentration, nicotine is a promising choice. McCarthy et al. (1987) measured indoor nicotine levels in smoking and nonsmoking homes. The home nicotine values ranged from an average of 0.1 $\mu g/m^3$ in the nonsmoking households to 4.2 $\mu g/m^3$ in the smoking households. The presence of low nicotine values in some of the nonsmoking households can be accounted for by visitors to the home who were smokers.

A number of studies have used integrated readings to determine nicotine levels in offices and public buildings. A selection of these studies are presented in Table 6.

Cigarettes are also known to be a source of cadmium. Lebret et al. (1987) considered cadmium as a useful tracer for ETS. They monitored twenty homes and one outdoor site for fine particulates in Watertown, MA. Particles were analyzed for elemental composition using x-ray fluorescence. At the outdoor site and in homes without smokers, cadmium levels were below the detectable limit. In homes with smokers, indoor cadmium levels were highly correlated with indoor fine particulate measurements.

Nitrosamines, some of which have been listed as animal carcinogens by the IARC, have been studied in public facilities and homes (Brunnemann et al., 1978). Using continuous measurements they found mean levels of nitrosamines in public facilities which ranged from 0.01 to 0.24 ng/L. Both homes monitored had levels of less than 0.005 ng/L.

Wallace et al. (1987) measured the personal exposure and breath levels of benzene and other aromatics in 200 smokers and 322 nonsmokers in New Jersey and California. Benzene is listed as a human carcinogen by the IARC (1986). They found a significant increase in breath concentration with the number of cigarettes smoked. Smokers were found to have up to 10 times the breath concentration of benzene compared to nonsmokers. Nonsmokers who reported smoke exposure at work showed elevated levels for fall and winter but not for spring and summer. The authors concluded that cigarettes were the major source of benzene for about 50 million U.S. smokers.

No single constituent of ETS is sufficient to completely characterize an individual's exposure to ETS. Research on ways to relate these measurements to specific health effects continues to be done. The most prudent course is to measure several of these components in exposure studies. Markers specific to the class of ETS components, or health outcome of interest, could be utilized in epidemiologic studies to enhance precision of the exposure.

Personal Exposures

Personal monitoring studies have many of the same problems that area monitoring has, such as trying to measure ETS exposure based on one or more markers. However, personal exposure monitoring has the advantage of including spatial and temporal dimensions to the measurements. It is also possible to use time-activity diaries to link exposure with location and activity.

The results of a personal monitoring study by McCarthy et al. (1987) show that the exposure of children to RSP was much higher than that of children from nonsmoking households. The average personal RSP value increased from 29 $\mu g/m^3$ for children from nonsmoking families to 56 $\mu g/m^3$ for children from smoking families. The average personal nicotine concentration increased from 0.3

$\mu g/m^3$ to $2.5\mu g/m^3$ for children from nonsmoking and smoking families respectively. A child's personal nicotine is highly correlated with the consumption of cigarettes in the home while the personal RSP was not. This implies that although there are multiple sources of RSP, the majority of ETS exposure is from the child's home.

Spengler et al. (1985) had 101 nonsmoking volunteers from Kingston/Harriman, Tennessee wear personal respirable suspended particulate monitors for 3 days. Nonsmokers were divided in two groups: those who lived with a smoker and those who did not. Outdoor and indoor particulate levels were taken for comparison. Results showed that personal exposure was not correlated with outdoor concentrations but that ETS significantly increased an individual's personal concentration profile.

In Spengler and Tosteson (1981), 45 nonsmoking adults were monitored for RSP for 18 days. They were also divided into two groups: those exposed to ETS and those who were not. Area monitors were also placed inside and outside. Personal exposure was higher than both indoor and outdoor measurements. On average, the individual exposure was increased by 20 $\mu g/m^3$ among those who reported exposure to ETS.

Cotinine is a major metabolite of nicotine. McCarthy et al. (1987) measured cotinine levels in the urine and saliva of 81 nonsmoking children. Nicotine levels in the air were also monitored as was RSP. They found a high correlation between personal nicotine levels and cotinine indicating a quantitative relationship may exist. They did however find high variability.

Coultas et al. (1987) measured cotinine in the saliva of 1360 nonsmoking children and adults. They found an increase with the number of smokers in the home at all ages. However, household variability was wide and even 30% of the nonsmokers living in a nonsmoking home had detectable cotinine levels.

Summary

1. Environmental tobacco smoke is the primary contaminant causing elevated RSP levels in enclosed spaces.

2. Environmental tobacco smoke can be a substantial contributor to the level of indoor air pollution concentration of benzene, acrolein, N-nitrosamine, pyrene and carbon monoxide.

3. Measured exposures to respirable suspended particulates are higher for nonsmokers who report exposure to ETS.

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FIGURES AND TABLES, CHAPTER 2

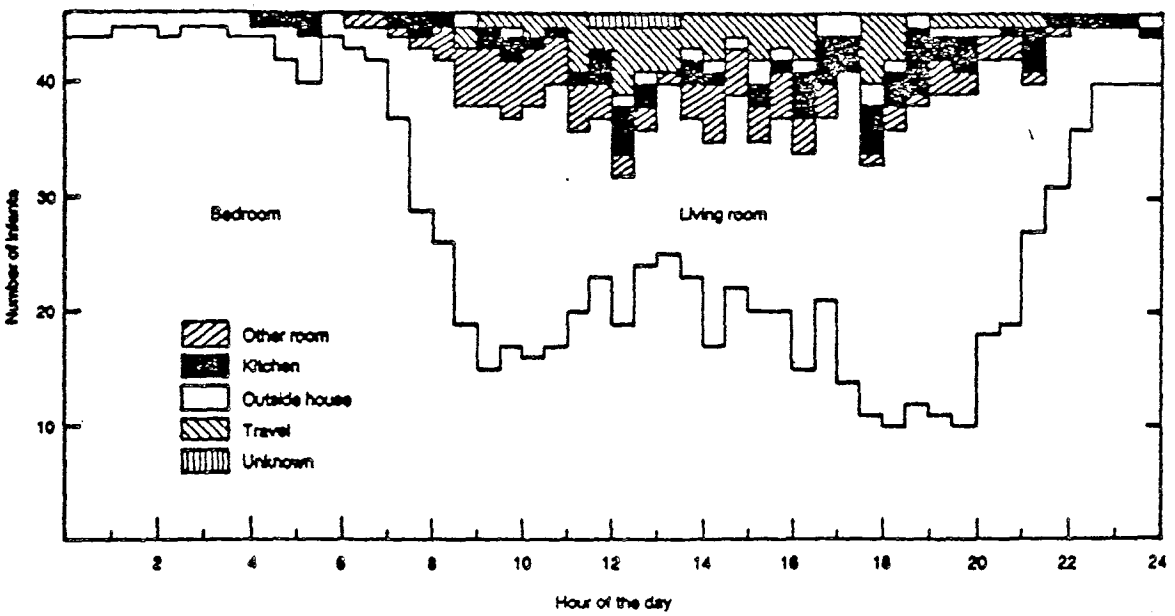

FIGURE 1. -Time Location Patterns for 46 Infants

Source: Harlos et al. (1987)

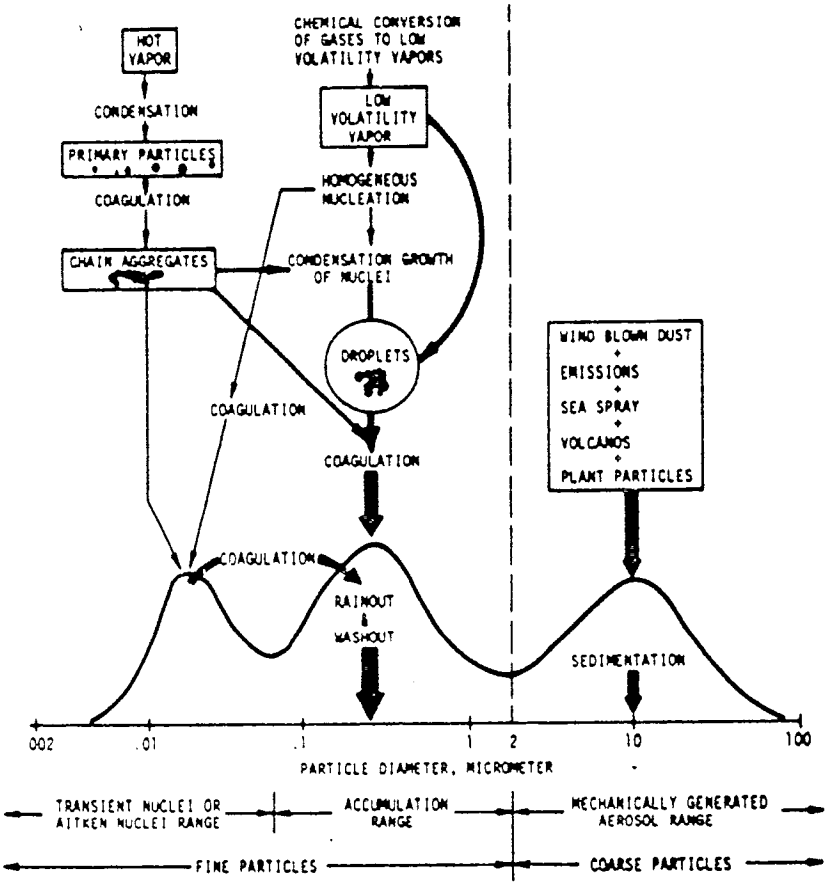

FIGURE 2. Schematic of an atmospheric aerosol surface area distribution showing the three modes, main source of mass for each mode, the princeipal process involved inserting mass into each mode, and the principal removal mechanisms.

Source: Whitby (1978)

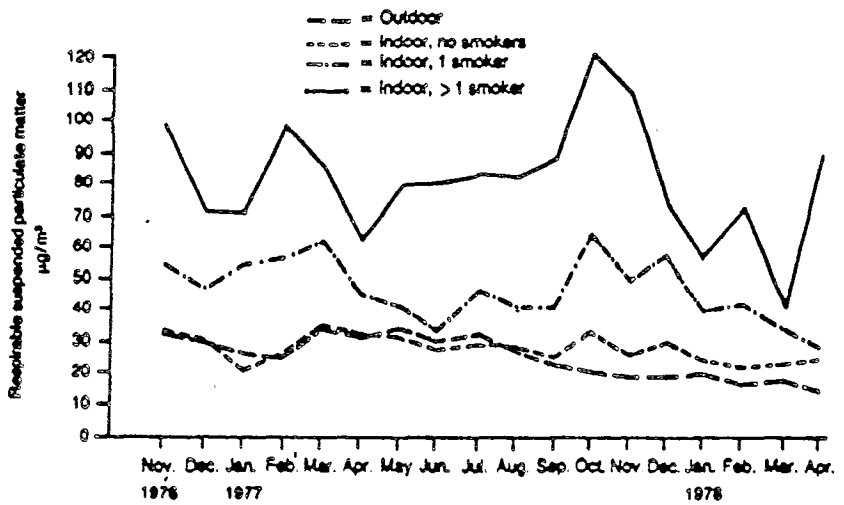

FIGURE 3. Monthly Mean Mass Respirable Particulate Concentrations ($\mu g/m^3$) Across Six Cities

Source: Spengler et al. (1981)

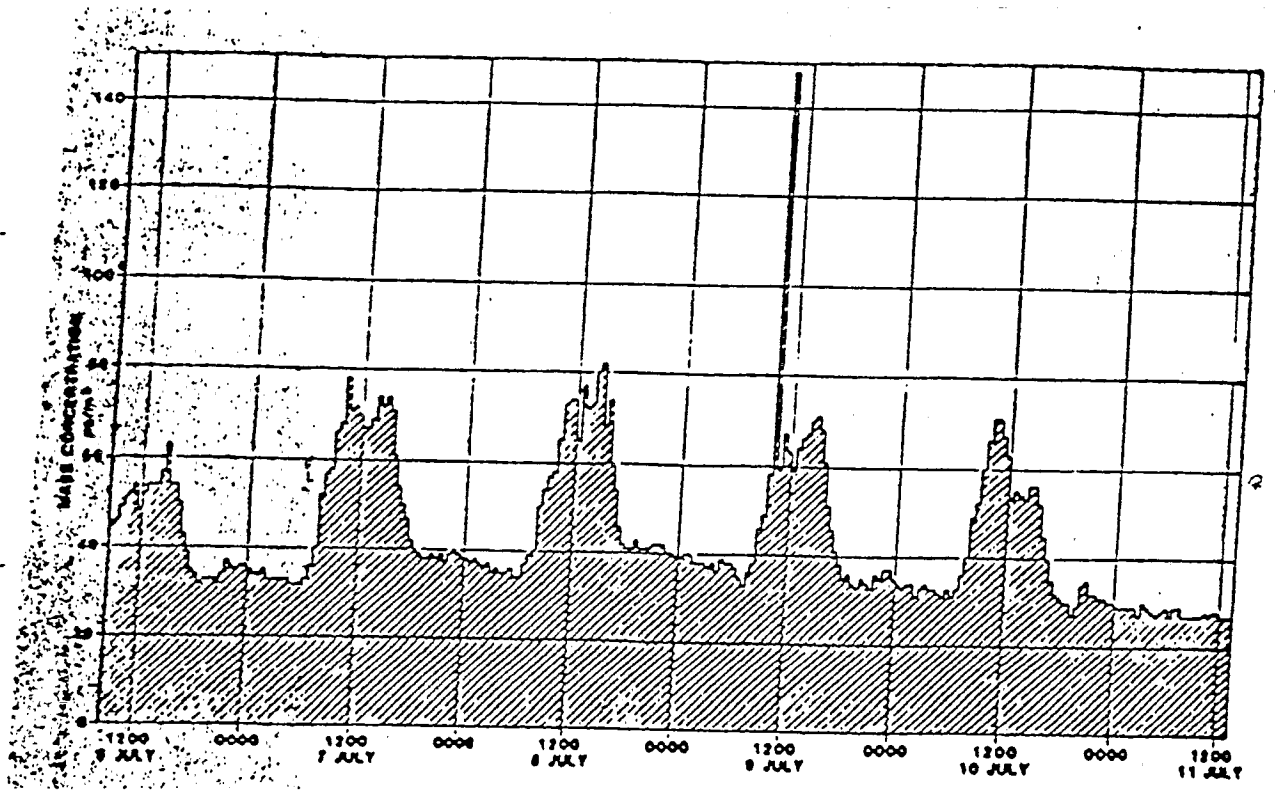

FIGURE 4. Aerosol Mass Concentration in R & D Office

Source: Quant et al. (1982)

TABLE 1. Mean Percent and Standard Deviation of Time Allocation in Various Locations by Work or School Classification Subgroup

Location	Homemaker	Student	Outdoor worker	Office/ Service	Industrial/ Construction	Total, all participants
Home	84.34 (2.02)[1]	60.91 (13.92)	49.97 (12.24)	68.74 (8.72)	57.28 (7.05)	64.21 (13.99)
Outside	5.52 (3.27)	8.62 (5.53)	19.81 (8.55)	2.47 (2.49)	10.59 (10.74)	8.08 (7.07)
Motor vehicle	4.28 (3.19)	5.11 (3.74)	8.67 (6.15)	4.69 (2.33)	7.64 (7.52)	5.51 (4.29)
Other indoors	6.01 (3.27)	23.61 (10.61)	21.55 (5.32)	24.99 (10.24)	24.80 (12.86)	21.58 (11.37)
Cooking	4.69 (1.88)	0.34 (0.79)	0.00 (0.00)	2.32 (2.30)	0.52 (0.86)	1.24 (1.98)
Near smokers	2.84 (4.32)	5.20 (7.88)	2.75 (3.38)	11.73 (15.19)	12.03 (10.05)	6.89 (9.71)
Number	8	32	4	12	8	66[2]

[1] Numbers in parentheses are the standard deviation.
[2] Two unemployed participants were included in the total, but not given a separate category.
SOURCE: Data from Quackenboss et al. (1982).

TABLE 2. Mean Percent Time Spent in Various Locations for Three Population Groups

phase	location	population group: workers	nonworkers	students	combined totals
summer	home (SD)	59.3 (11.9)	75.2 (12.1)	68.3 (12.5)	65.4 (13.3)
	outside (SD)	12.3 (9.1)	12.9 (9.9)	15.0 (9.3)	13.7 (9.4)
	motor vehicle (SD)	5.8 (4.2)	4.4 (2.7)	3.3 (4.3)	4.4 (4.3)
	work/school (SD)	15.5 (10.9)	0.2 (0.8)	4.4 (7.8)	8.4 (10.6)
	other indoors (SD)	7.0 (6.4)	7.2 (6.4)	9.0 (9.6)	8.1 (8.2)
	N	137	32	177	346
winter	home (SD)	66.1 (11.4)	83.3 (8.4)	66.1 (10.1)	67.5 (11.5)
	outside (SD)	3.3 (5.35)	1.9 (2.0)	3.9 (3.3)	3.5 (4.2)
	motor vehicle (SD)	5.6 (5.6)	4.3 (2.5)	3.3 (2.6)	4.2 (4.1)
	work/school (SD)	18.6 (10.4)	3.0 (7.1)	19.5 (7.5)	17.9 (9.7)
	other indoors (SD)	6.4 (6.0)	7.6 (5.3)	7.3 (6.2)	7.0 (6.1)
	N	127	26	176	329

Source: Quackenboss et al. (1986)

TABLE 3. Distribution of Constituents in Mainstream Smoke (MS) and the Ratio of Sidestream Smoke (SS) to MS of Nonfilter Cigarettes

Vapor phase constituents[1]	MS range	SS/MS ratio	Particulate phase constituents[1]	MS range	SS/MS ratio
Carbon monoxide	10–23 mg	2.5–4.7	Particulate matter[2]	15–40 mg	1.3–1.9
Carbon dioxide	20–40 mg	8–11	Nicotine	1–2.5 mg	2.6–3.3
Carbonyl sulfide	18–42 µg	0.03–0.13	Anatabine	2–20 µg	<0.1–0.5
Benzene[3]	12–48 µg	10	Phenol	60–140 µg	1.6–3.0
Toluene	160 µg	6	Catechol	100–360 µg	0.6–0.9
Formaldehyde	70–100 µg	0.1–≈50	Hydroquinone	110–300 µg	0.7–0.9
Acrolein	60–100 µg	8–15	Aniline	360 ng	30
Acetone	100–250 µg	2–5	2-Toluidine	160 ng	19
Pyridine	16–40 µg	6.5–20	2-Naphthylamine[3]	1.7 ng	30
3-Methylpyridine	12–36 µg	3–13	4-Aminobiphenyl[3]	4.6 ng	31
3-Vinylpyridine	11–30 µg	20–40	Benz[a]anthracene[4]	20–70 ng	2–4
Hydrogen cyanide	400–500 µg	0.1–0.25	Benzo[a]pyrene[3]	20–40 ng	2.5–3.5
Hydrazine[3]	32 ng	3	Cholesterol	22 µg	0.9
Ammonia[5]	50–130 µg	40–170	γ-Butyrolactone[4]	10–22 µg	3.6–5.0
Methylamine	11.5–28.7 µg	4.2–6.4	Quinoline	0.5–2 µg	8–11
Dimethylamine	7.8–10 µg	3.7–5.1	Harman	1.7–3.1 µg	0.7–1.7
Nitrogen oxide	100–600 µg	4–10	N'-Nitrosonornicotine[6]	200–3,000 ng	0.5–3
N-Nitrosodimethylamine[4]	10–40 ng	20–100	NNK[6]	100–1,000 ng	1–4
N-Nitrosopyrrolidine[4]	6–30 ng	6–30	N-Nitrosodienthanolamine[4]	20–70 ng	1.2
Formic acid	210–490 µg	1.4–1.6	Cadmium	100 ng	7.2
Acetic acid	330–810 µg	1.9–3.6	Nickel[3]	20–80 ng	13–30
			Zinc	60 ng	6.7
			Polonium-210[2]	0.04–0.1 pCi	1.0–4.0
			Benzoic acid	14–28 µg	0.67–0.95
			Lactic acid	63–174 µg	0.5–0.7
			Glycolic acid	37–126 µg	0.6–0.95
			Succinic acid	110–140 µg	0.43–0.62

[1] Values are given for fresh and undiluted MS and SS.
[2] Human carcinogen (IARC 1986).
[3] Suspected human carcinogen (IARC 1986).
[4] Animal carcinogen (IARC 1986).
SOURCE: Elliott and Rowe (1975); Hoffmann et al. (1983); Klus and Kuhn (1982); Sakuma et al. (1983); Sakuma, Kusama, Yamaguchi, Matsuki et al. (1984); Sakuma, Kusama, Yamaguchi, Sugawara (1984); Schmeltz et al. (1975).

TABLE 4. Respirable Particulate Levels as a Function of Number of Smokers

Smoker status	Number	Mean (μg/m³)	Standard deviation
No smokers	35 homes/1,186 samples	24.4	11.6
1 smoker	15 homes/494 samples	36.5	14.5
2 smokers	5 homes/153 samples	70.4	42.9
2+ smokers	4 homes/7 samples	51.8	12.3

SOURCE: Spengler et al. (1981).

TABLE 5. Particulates Measured under Realistic Conditions

Study	Type of premises	Occupancy (active smokers per 100 m³)	Ventilation	Monitoring conditions (min)	Levels (µg/m³) Mean	SD	Nonsmoking controls (µg/m³) Mean	SD
Repace and Lowrey (1980)	Cocktail party	0.75	Natural	15	351	± 38	24	
	Lodge hall	1.26	Mechanical	50	697	± 28	60[1]	
	Bar and grill	1.78	Mechanical	18	589	± 28	63[1]	
	Firehouse bingo	2.77	Mechanical	16	417	± 63	51[1]	
	Pizzeria	2.94	Mechanical	32	414	± 58	40[1]	
	Bar/cocktail lounge	3.24	Mechanical	26	334	± 120	50[1]	
	Church bingo game	0.47	Mechanical	42	279	± 18	30	
	Inn	0.74	Mechanical	12	239	± 9	22[1]	
	Bowling alley	1.53	Mechanical	20	202	± 19	49[1]	
	Hospital waiting room	2.15	Mechanical	12	187	± 52	58[1]	
	Shopping plaza restaurant							
	Sample 1	0.18	Mechanical	18	153	± 8	59[1]	
	Sample 2	0.18	Mechanical	18	163	± 4	36[1]	
	Barbeque restaurant	0.89	Mechanical	10	136	± 17	40[1]	
	Sandwich restaurant A							
	Smoking section	0.29	Mechanical	20	110	± 36	40[1]	
	Nonsmoking section	0	Mechanical	20	55	± 5	30	
	Fast-food restaurant	0.42	Mechanical	40	109	± 36	34[1]	
	Sports arena	0.09[2]	Mechanical	12	94	± 13	55[1]	
	Neighborhood restaurant/bar	0.40	Mechanical	12	93	± 17	55[1]	
	Hotel bar	0.59	Mechanical	12	93	± 2	30	
	Sandwich restaurant B							
	Smoking section	0.13	Mechanical	8	86	± 7	55	
	Nonsmoking section	0	Mechanical	21	51			
	Roadside restaurant	1.12	Mechanical (9.5 ach[3])	18	107[4]		30	
	Conference room	3.54	Mechanical (4.3 ach[3])	6	1947[4]		55	
Repace and Lowrey (1982)	Dinner theater	0.14	Mechanical	44	145	± 43	47	± 10
	Reception hall	1.19	Mechanical	20	301	± 30	33[1]	
	Bingo hall	0.93[2]	Natural	2	1140		40[1]	
		0.93[2]	Mechanical (1.39 ach[3])	6	443[4]		40[1]	

[1] Sequential outdoor measurement (5 minute average).
[2] Estimated.
[3] Air changes per hour.
[4] Equilibrium level as determined from concentration vs. time curve.

SOURCE: U.S. Department of Health and Human Services (1986)

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TABLE 6. Nicotine Measured Under Realistic Conditions

Study	Type of premises	Occupancy	Ventilation	Monitoring conditions	Levels (μg/m³) Mean	Levels (μg/m³) Range	Nonsmoking controls Mean	Nonsmoking controls Range
Badre et al. (1978)	6 cafes	Varied	Not given	50 min sample		25–52		
	Room	18 smokers	Not given	50 min sample	500			
	Hospital lobby	12 to 30 smokers	Not given	50 min sample	37			
	2 train compartments	2 to 3 smokers	Not given	50 min sample		36–50		
	Car	3 smokers	Natural, open	50 min sample	65			
			Natural, closed	50 min sample	1010			
Cano et al. (1970)	Submarines 66 m³	157 cigarettes per day	Yes		32 μg/m³			
		94–103 cigarettes per day	Yes		15–35 μg/m³			
Harmsen and Effenberger (1967)	Train	Not given	Natural, closed	30–45 min samples		0.7–3.1		
Hinds and First (1975)[1]	Train	Not given	Not given	2¼ hr samples	4.9		Values not given	
	Bus	Not given	Not given	2¼ hr samples	6.3		Values not given	
	Bus waiting room	Not given	Not given	2¼ hr samples	1.0		Values not given	
	Airline waiting room	Not given	Not given	2¼ hr samples	3.1		Values not given	
	Restaurant	Not given	Not given	2¼ hr samples	5.2		Values not given	
	Cocktail lounge	Not given	Not given	2¼ hr samples	10.3		Values not given	
	Student lounge	Not given	Not given	2¼ hr samples	2.8		Values not given	
Weber and Fischer (1980)[2]	44 offices	Varied	Varied	140 × 3 hr samples	0.9 ± 1.9	13.8 (peak)	Values not given	
First (1984)	1 public building	Nonsmokers	Mechanical	Not given			5.5	
	8 public buildings	1 to 5 smokers	Natural and mechanical	Not given	13.2	2.7–30.0		
Muramatsu et al. (1984)	Office	Not given	Not given	Not given	19.4	9.3–31.6		
	Office	Not given	Not given	Not given	22.1	14.6–28.1		
	Laboratory	Not given	Not given	Not given	5.8	1.8–9.6		
	5 conference rooms	Not given	Not given	Not given	38.7	16.5–53.0		
	3 houses	Not given	Not given	Not given	11.1	7.6–14.6		
	Hospital lobby	Not given	Not given	Not given	3.0	1.9–5.0		
	4 hotel lobbies	Not given	Not given	Not given	11.2	5.5–18.1		
	5 restaurants	Not given	Not given	Not given	14.8	7.1–27.8		
	3 cafeterias	Not given	Not given	Not given	26.4	11.6–42.2		
	3 bus and railway waiting rooms	Not given	Not given	Not given	19.1	10.1–36.4		
	4 cars	Not given	Not given	Not given	47.7	7.7–83.1		
	8 trains	Not given	Not given	Not given	16.4	8.6–26.1		
	7 airplanes	Not given	Not given	Not given	15.2	6.3–26.8		

[1] Background levels have been subtracted.

[2] Control values (unoccupied rooms) have been subtracted.

SOURCE: U.S. Department of Health and Human Services (1986)

CHAPTER 4

ABSORPTION OF SMOKE CONSTITUENTS BY NONSMOKERS

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INTRODUCTION

Exposure to environmental tobacco smoke (ETS) occurs at the worksite, in public places, and in private homes. ETS is a composite of effluents generated in various ways during the burning of tobacco products. The major source for ETS is sidestream smoke (SS) which is formed during smouldering of cigarettes, cigars and pipes between the taking of puffs. Minor contributions to ETS are made by those pollutants of the mainstream smoke (MS) that are exhaled after inhalation of each puff by the active smoker. The smoke escaping into the air from the burning cone and from the mouthpiece of a tobacco product during and after puff-drawing is another minor contributor, in addition there is some diffusion of MS gas phase components through the cigarette paper into the environment. More information is needed on the relative sources of smoke in the complex mixture of ETS generated from different cigarettes under varying conditions.

In the laboratory, MS and SS are generated under standardized conditions by machine smoking (1,2). While these conditions enable us to compare the yields of individual smoke constituents from various brands of cigarettes, cigars and pipe tobacco, they do not fully reflect the patterns of smoking by humans (3,4). The consumer's intensity of puff-drawing and inhaling of the smoke is profoundly influenced by the nicotine content of the MS (4,5), and smoking intensity is highest when cigarettes with perforated filter tips are being smoked (6).

The SS release is governed by the velocity of air currents around the burning cone; thus, higher air flow generates higher yields of most SS components. Even though a major reduction of mainstream smoke yields of the sales-weighted average cigarettes has occurred during the last three decades, (U.S. cigarettes declined from 35.5 mg tar in 1954 to 12 mg tar in 1983; (7)), the SS emissions of smoke constituents were not significantly reduced (8,9). The data in Table 1 emphasize this with a comparison of the yields of a select group of toxic compounds in the MS and SS of four types of U.S. cigarettes. These cigarettes were machine-smoked under identical conditions. Since the consumer of the low-yield filter cigarettes is likely to smoke more intensely, a

larger portion of the tobacco column is burned during smoking of this type of cigarette than is burned during smoking of nonfilter cigarettes. Therefore, a somewhat lower yield of SS is expected from the low-yield cigarette smoked by the consumer than is obtained by its standardized machine smoking.

The exposure of nonsmokers to the effluents of burning tobacco products usually occurs after considerable dilution of these air pollutants. This is well substantiated by analyses of the air in enclosed spaces polluted by tobacco smoke (10,11).

A. Biological Markers in Physiological Fluids

The exposure of nonsmokers to ETS can be assessed with the help of questionnaires, by estimating the dose from the chemical analysis of smoke-polluted air, by personal monitoring of ETS components and/or by measuring the uptake of individual smoke components in physiological fluids of individuals during or after exposure. The last and most promising method will be discussed in this chapter.

The degree of exposure to ETS depends on several factors, including length of time spent in a smoke-polluted area, the number of smokers within this area, the size and nature of the space, the degree of ventilation and the respiratory rate of the exposed individual. Thus, optimal assessment of ETS exposure is achieved by analysis of physiological fluids of exposed individuals as well as by analysis of the respiratory environment. New biochemical methods enable us to quantify exposure to ETS by determining the uptake of certain smoke contstituents (or their metabolites) in biological fluids. An primary requirement for such biochemical measurements is the availability of highly sensitive and specific methods.

1. Nicotine and Cotinine.

Disregarding accidental or occupational exposure to tobacco (12,13), or the use of nicotine-containing chewing gum or nicotine aerosol rods as aids for smoking cessation (14), the presence of nicotine and of its major metabolites in physiological fluids is entirely due to the exposure to tobacco, tobacco smoke, or ETS. Low levels of nicotine have been found in other members of the solanaceous variety of plants (14A) but could not be expected to make an impact on the body burden of nicotine which is obtained from tobacco sources. Nicotine and its major metabolite, cotinine, in saliva, blood or urine of active smokers and of passively exposed nonsmokers are primarily determined by gas chromatography (GC) with a nitrogen-sensitive detector, and by radioimmunoassay (RIA) (15-17). An HPLC method which has been developed for quantitation of cotinine in plasma or saliva of smokers (18) has not been applied to urine analysis even though the analysis of this biological fluid appears to have the greatest potential for

evaluation of nicotine uptake by nonsmokers. A problem with this HPLC method seems to be an unusually high background of cotinine in persons reporting no exposure to ETS. The possibile co-migration of caffeine with cotinine in this system needs to be excluded. (18A) A recently published, highly sensitive method for determining nicotine in plasma by HPLC with dual electrochemical detection (2 ng/ml) has not as yet been applied to physiological samples of involuntary smokers (19). Another emerging analytical method for the determination of nicotine or cotinine is the enzyme-linked immunosorbent assay (ELISA; 20).

Trans-3'-hydroxycotinine has been found to be the most abundant nicotine metabolite in the urine of active smokers (21), however, it is difficult to quantitate. Since the compound is not readily soluble it has to be transformed into a heptafluoro derivative prior to GC detection (22). The levels of 3'-hydroxycotinine in plasma have been found to be much lower than those of cotinine in the same smokers although the renal excretion of 3'-hydroxycotinine has been reported to be greater (23). Despite its abundance in urine of smokers, this compound has not yet been applied to the analysis of ETS uptake by nonsmokers.

The GC and RIA methods are most widely used for assaying nicotine and cotinine in active as well as in passive smokers, primarily because of their specificity and sensitivity, and because the needed instrumentation is available in most modern laboratories. Chromatographic methods, especially those using GC with nitrogen-phosphorus detectors (detection limit 0.1 ng/ ml fluid; 16), or a mass-spectral detection system, offer greatest specificity and high sensitivity; however, they require expensive instrumentation and technical expertise and they are rather labor intensive. Since the air as well as glassware in laboratories may contain traces of nicotine, the chromatographic methods require the utmost precautions to avoid contamination of samples.

The RIA techniques are operationally simpler, less expensive and require smaller samples (detection limit 0.35 ng/sample; 17). More than 50 nicotine metabolites and structurally-related molecules have been tested as inhibitors of nicotine and cotinine antigen-antibody reactions; few of them interfere with the RIA (24). Nevertheless, the potential for cross-reactivity with unknown endogenous components exists. The fact that, upon analysis, thousands of samples obtained from nonsmokers in the US and UK have been found to be negative, indicates that diets and drugs commonly used in these two countries do not pose problems of interference. There is good correlation between results obtained by GC and RIA analysis for plasma cotinine concentrations (r=0.99; 25). A potential problem in RIA analysis can come from extrapolation to values below the linear range of the standard curve. Care must always be taken to insure proportionality of response.

An interlaboratory comparison of data from 11 laboratories in 6 countries has demonstrated that GC and RIA techniques can reliably quantitate nicotine and cotinine in urine and plasma samples. A good correlation of laboratory methods was observed in plasma samples and in urine samples to which cotinine had been added as a tracer. However, in urine samples without tracer, several RIA values for cotinine were found to be slightly higher than those observed by GC. This could be due to a cross reaction of the antibody with another compound present in urine, or the discrepancy could arise from a loss of urinary cotinine during GC extraction. The former explanation is more likely to apply here although conventional GC extraction techniques have been reported to result in the loss of conjugated metabolites of nicotine. The quantitation of these conjugated compounds by GC methods has recently been reported by Curvall et al. (25a). In addition cross reactivity of various cotinine antibodies with trans-3'hydroxycotinine has been reported to range from 2% (J.J. Langone, pers. comm.) to 30%; (25b)) All immunoassay methods have led, however, to perfect distinction between nonsmokers and active smokers (26).

Table 2 presents data from model studies on the uptake of ETS by nonsmokers under acute exposure conditions (27-30). The main purpose of these assays was to develop the methodology for field studies and to compare the uptake of nicotine from environments with various degrees of pollution and different types of pollutants under controlled conditions. It has been shown that the equilibrium of nicotine between vapor phase and particulate phase of ETS depends greatly on the concentration and pH of the emitted smokestream (31) and, thus, influences the uptake of nicotine by inhalation.

After repeated exposure to ETS under controlled conditions, such as twice daily 80-minute exposure on 3 consecutive days to the diluted pollutants of 4 concurrently smoked cigarettes (32), the measurements in 4 nonsmokers have shown that except for nicotine in the saliva, the physiological fluids do not reflect maximal concentrations of nicotine and cotinine until at least 24 hours later. This observation has led to comparisons of the elimination of cotinine in smokers and nonsmokers exposed to ETS (33). The elimination half-life ($t_{1/2}$) of cotinine from the urine of smokers took 21.9 hours and 32.7 hours for nonsmokers. In a second assay, five cigarette smokers were asked to abstain from tobacco use for 5 days and were then given nicotine gum for three days. After another 8 days of abstinence from nicotine, the volunteers were exposed to sidestream smoke (SS). At this point, the cotinine elimination ($t_{1/2}$) from urine (ng/ml) by smokers took 15.4 hours, by nicotine gum users 18.2 hours, by 8-day exsmokers 27.5 hours, and by the never-smokers 25.6 hours (33). These findings suggest that the residence times of nicotine, cotinine and other tobacco alkaloids, are likely related to the route of nicotine uptake as well as to possible differences in metabolism between smokers and

nonsmokers. The longer elimination time for cotinine in nonsmokers has been confirmed by other study groups (35-37), however, the observation has also been challenged (38,39). A longer residence time of nicotine metabolites in nonsmokers could conceivably increase the possibility of endogenous formation of carcinogenic N-nitrosamines (40).

Most importantly, differences in the elimination times of cotinine from urine preclude a direct extrapolation to "cigarette equivalents of smoke uptake" by comparing the levels of cotinine excreted by active and passive smokers. This has been discussed by some investigators (10).

Table 3 includes comparisons of nicotine and cotinine in physiological fluids of nonsmokers with or without ETS exposure, and of active cigarette smokers in England (41). Data on the uptake of nicotine by involuntary smokers from additional studies are summarized in Table 4 (29,42-54). Most of these studies demonstrate that nicotine and cotinine levels in physiological fluids of involuntary smokers generally amount to 1 percent and reach maximally a few percent of the amounts determined in active cigarette smokers. Data by Matsukura et al. from Japan on the other hand, show exceptionally high levels of cotinine in the urine of passive smokers. This may be due to several factors including differences in the design of studies and measurement methods (26). Aside from differences in methodology one cannot rule out that differences in the uptake and metabolism of nicotine which have been observed in various population groups, and diet may be partially responsible for the exceptional data reported in the Japanese study (47). A recent finding indicates that the urinary excretion rates of Japanese smokers were significantly different from those determined in adult cigarette smokers in Europe and North America (55). Additionally, a large epidemiological study in the U.S. has demonstrated significant differences in serum cotinine levels between Black and White smokers after adjustment for cigarettes smoked per day and daily nicotine availability (55a).These differences in nicotine metabolism require further thorough investigation.

Survey data on exposure at home, in the workplace and on social occasions were collected from 319 employed subjects and were correlated with levels of cotinine in a random urine sample. Mean urine/cotinine/creatinine levels were higher for women than for men possibly due to differences in creatinine excretion between the sexes. It is also noteworthy that 94% of the women were employed indoors. Higher levels of urinary cotinine were noted in both men and women who lived with a smoker than in those subjects who did not report living with a smoker (13.3±2.4 vs 5.1±0.4 in men and 13.9±1.9 vs. 5.6±0.6 in women). Differences in the prevalence of exposure at home existed between sexes (males 13.5% vs. females 29.2%). Levels of cotinine found across different exposures indicate that home exposure has a more pronounced effect on urine

cotinine than does workplace exposure (Table 5; 55b).

The nicotine uptake by infants due to ETS exposure, caused by smoking mothers or caretakers, appears to be higher than that observed in adult passive smokers. The amount of cotinine excreted in the urine of the infants was correlated with the number of cigarettes smoked by the mother, or caretaker or other persons, during the 24 hours preceding the measurement (33). The primary determinant of urinary cotinine levels has been found to be the smoking behavior of the mother. The finding of relatively high uptake of ETS, as determined by nicotine/cotinine concentrations in the urine of infants, is in line with the observation that infants of smokers have higher rates of respiratory infections than infants in nonsmokers' homes (56).

Analytical data on nicotine and cotinine in physiological fluids of nonsmokers can be misleading in a few cases. These pertain to the very light smokers and those nonsmokers who either chew tobacco or use oral snuff. It is possible, though rare, that the very light smoker shows nicotine/cotinine levels approaching those of passive smokers with extremely high ETS exposure. When used in combination with cotinine measurements, COHb analyses can help to differentiate between the two groups. In regular consumers of snuff or chewing tobacco, cotinine levels are comparable to those found in cigarette smokers while thiocyanate levels and COHb values remain low (57).

The determination of nicotine and cotinine in hair has been tried in an attempt to differentiate between active and passive smokers (58). This determination revealed higher nicotine concentrations in the hair of smokers than in the hair of ETS-exposed nonsmokers and documented the absence of cotinine, the major metabolite of nicotine, within the hairshaft of nonsmokers. Hair sampling for determining ETS-exposure of nonsmokers deserves more thorough investigation.

In summary, in the hands of experienced biochemists, the determination of nicotine and, especially, of cotinine in saliva, serum and/or urine in involuntary smokers represents a reliable, specific method for assaying the level of uptake of ETS by nonsmokers. The choice of biological fluid for the quantitation of cotinine depends upon the question asked. For the evaluation of changes in smoking behavior, serum or urine are preferred while saliva is sufficient to determine whether or not a subject is a smoker (59). For studies of ETS exposure, it is often impractical to collect serum by venipuncture, and since nicotine concentration in saliva can be extremely high immediately following ETS exposure, several hours must pass before the concentration of cotinine in saliva is stabilized (30). Also, when large numbers of subjects are to be evaluated, it is preferable to avoid invasive procedures which might discourage participation and possibly bias the results.

Measurements of cotinine in urine and saliva have been successfully used to quantitate ETS exposure in large populations. Cotinine excretion in urine is independent of pH, while nicotine excretion is greatly influenced by it. At values above pH 6.0, resorption of nicotine from the urine occurs especially during longer residence time in the bladder. Cotinine is not subject to resorption and, as far as it has been investigated, 3'-hydroxycotinine, a second major nicotine metabolite, is also not affected (60).

Quantitation of cotinine in random urine samples can have methodological problems relative to the volume of urine excreted in any given time period as well as dilution effects. The ideal standard for evaluation of cotinine excretion in urine would be the analysis of a 24-hour urine sample. Since this is impractical in epidemiological studies, random urine samples are usually collected at the time a questionnaire is administered. In this case, the ratio of cotinine to creatinine in a given sample is often used to allow for differences in urine dilution. Urinary creatinine excretion is usually constant from day to day for a given individual, but it does vary among individuals. As a reflection of muscle mass it is generally excreted at about 1 g per day (men, 1.1 to 3.2 g/day; women, 0.9 to 2.5 g/day). In older persons, the excretion of creatinine may decrease to 0.5 g/day. Low levels of creatinine may also be found in dehydrated infants; this necessitates caution in the expression of ng cotinine/mg creatinine in a random sample (35). However, a recent study with pre-school children has shown that cotinine/creatinine ratios in passively exposed children 'track' over several weeks and reflect questionnaire data on exposure (61). Epidemiological studies in adults have also shown good correlations between self-reported indices of exposure and cotinine/creatinine ratios when data for men and women are analyzed separately.(55b)

2. Carbon Monoxide. Carbon monoxide (CO) is formed during the combustion of organic matter including the burning of a tobacco product. It is also produced in vivo during metabolic processes. Endogenous CO results primarily from the breakdown of heme-containing proteins such as hemoglobin. In nonsmokers who are not exposed to industrial pyrolysis products or vehicle emissions, the baseline levels of CO, present in the bloodstream as carboxyhemoglobin (COHb), are generally below 1.5% of the total hemoglobin.

Persons exposed to heavy vehicle emissions can have COHb levels up to about 2.5%. In cigarette smokers, COHb levels were found to average 5.7% in a study of 450 smokers (62) with little difference being noted between smokers of high- or low-yield products. This value is similar to that of 4.7% found in middle aged men in a study by Wald et al. (63).

Carboxyhemoglobin levels are not good indicators of ETS

uptake, due to the fact that CO exposure is not limited to tobacco smoke; in addition, the measurement of COHb is relatively insensitive. A study in England did not find significant differences in COHb levels in subjects reporting no exposure, some exposure, or a lot of exposure (64). This was confirmed by others (65) and also by a controlled chamber assay (61). One study in which significant elevations of COHb were found used controlled exposure to tobacco smoke at a level of 25 ppm CO for 8 hours. This intense exposure resulted in an average increase of COHb levels by 2.5% (85). However, such results are not applicable to free-living situations in field studies (67).

3. Thiocyanate. Hydrogen cyanide, absorbed from tobacco smoke is detoxified in the liver to thiocyanate (SCN-). Measurement of SCN- has been used to differentiate smokers from nonsmokers or, as mentioned earlier, in combination with nicotine-cotinine assays to distinguish smokers from chewers of tobacco. Thiocyanate can also be derived from the diet, cruciferous vegetables being an excellent source (68). The specificity of SCN as a marker of tobacco smoke inhalation is poor and it is generally difficult to distinguish light smokers from nonsmokers. This lack of specificity makes SCN- unsuitable for the evaluation of ETS uptake by nonsmoking subjects.

4. Hydroxyproline. Japanese investigators have studied the excretion of hydroxyproline in persons exposed to ETS as well as in active smokers and in persons exposed to high levels of air pollutants (69). The rationale for these studies is that the inhalation of nitrogen dioxide causes degradation of lung collagen and elastin which results in urinary excretion of hydroxyproline. The investigations of the Japanese group suggested an elevated excretion of hydroxyproline by children of smoking parents as well as by wives of smoking husbands, active smokers, and individuals exposed to vehicle emissions. Since NOx levels in ETS are relatively low by comparison to mainstream smoke or vehicle emissions (56,70,71), such increased elimination of hydroxyproline in passively exposed persons seemed surprising. In fact, another group of investigators has been unable to confirm this finding (72).

5. N-Nitroso-Amino Acids. The occurrence of endogenous nitrosation reactions in cigarette smokers has been demonstrated in several studies. This phenomenon entails the risk of endogenous formation of carcinogenic N-nitrosamines. Endogenous formation of N-nitrosamines has been proven by urinary excretion of the noncarcinogenic N-nitrosoproline (NPRO), N-nitrosothioproline (NTPRO), and N-nitrosomethylthioproline (NMTPRO). Whereas the average excretion of NPRO in nonsmokers amounted to 2.0±1.5 ug/24 hrs, cigarette smokers excreted an average of 7.0±4.0 ug/24 hrs (73-77). In the case of NTPRO, the average urinary excretion by nonsmokers (ug/24 hrs) was 5.9, that by cigarette smokers 8.7 and that of NMTPRO was 5.6 and 8.5, respectively (75). Only two studies have explored the possibility that endogenous formation of

N-nitrosamino acids may also be increased in involuntary smokers (77,78).

The data for NPRO in the urine of a limited number of involuntary smokers were not different from NPRO data for nonsmokers without ETS-exposure. A carefully designed study with a larger number of passive smokers may prove that the average value for NPRO or, more likely, for NTPRO is higher in ETS- exposed nonsmokers than in those without ETS-exposure. Controlled long-term exposures at high levels of ETS have not measured NPRO or NTRO and such studies might show a value for NPRO or, more likely, for NTPRO that is higher in ETS-exposed nonsmokers than in those without ETS exposure. However, it is unlikely that the determination of N-nitrosamino acids in urine would ever lead to an assay for personal dosimetry of ETS-exposure in free-living subjects.

6. Aromatic Amines. The sidestream smoke of cigarettes contains significantly larger quantities of aromatic amines than the mainstream smoke. For example, the MS of a nonfilter cigarette contains 0.36 ug aniline and 0.16 ug of 2-toluidine, whereas the SS of the same cigarette releases 10.8 ug of aniline and 4.1±3.2 ug of 2-toluidine (79). The urine of cigarette smokers contains somewhat higher amounts of aromatic amines than the urine of nonsmokers. The 24-hour urine void of cigarette smokers contains 3.1±2.6 ug aniline and 6.3±3.7 ug 2-toluidine, while the urine of nonsmokers contains 2.8±2.5 ug aniline and 4.1±3.2 ug 2-toluidine (80). The levels of metabolites of these aromatic amines are expected to be markedly higher in the urine of smokers than of nonsmokers. Confirmation of the significance of this difference would encourage the development of analytical dosimetry for evaluation of the impact of ETS-exposure on urinary excretion of the metabolites of aromatic amines.

7. Thioethers in Urine. Cigarette smokers excrete higher amounts of thioethers than do nonsmokers (81). A study of 26 cigarette smokers showed mean urinary thioether values of 4.3±0.4 mmol/mol creatinine compared to an equivalent mean value for 10 nonsmokers of 2.8±0.2 mmol/mol creatinine (82).

In another study nonsmokers were placed on a controlled diet and were subjected to 8-hr ETS-exposure at two levels of concentration. Prior to ETS exposure 10 nonsmokers excreted 40.0±15.4 umol thioethers/24 hrs. The levels rose to 53.9±22.8 umol after exposure to ETS dose 1 (10 ppm CO). At a higher dose level (20-22 ppm CO), pre-exposure values were 69.3±36.3 and post-exposure levels 90.7±44.8. The 10 cigarette smokers who smoked 20 cigarettes each during 8 hrs in order to provide the ETS pollution in the chamber showed an increase of thioether excretion from 89.1±24.8 to 136.1±38.9 umol/24 hrs (67). In other words, the urinary thioether excretion of the passive smokers in this study increased up to 45% and, in the case of the active smokers with the same ETS exposure it increased about 50- 65%. These findings

require confirmation but they appear to indicate that the thioether analysis of the urine will most likely not be suitable for the determination of the ETS uptake by involuntary smokers due to varying background levels across subjects.

B. Genotoxicity of Physiological Fluids

Several studies have explored the possibility that physiological fluids of cigarette smokers contain significantly higher amounts of genotoxic agents than those of nonsmokers (81). The most extensive data base in this field has shown significantly higher mutagenicity in the Salmonella thyphimurium assay of urine of cigarette smokers compared to those of nonsmokers. Since the original study by Yamasaki and Ames in 1977 (83) at least 20 investigations have shown that the urine of cigarette smokers is significantly more mutagenic than the urine of nonsmokers who are not exposed to genotoxic agents in occupational environments. But it has also been shown that the mutagenicity of the urine of smokers can be effected by diet (84). It has further been surmised that exposure of nonsmokers to ETS may lead to increased urinary excretion of mutagens. Of the 6 published studies in which the urine of passive smokers was tested for mutagenicity with the Ames test, 3 showed increased activity and 3 showed no increase or, at the most an insignificant increase in mutagenic activity (81,85-87).

C. Adduct Formation of Carcinogens in Passive Smokers.

Measurements in physiological fluids of nicotine and its major metabolite, cotinine, have been shown to be objective indicators of the uptake of ETS. However, these assays will not reflect an individual's response to specific ETS carcinogens. That information is best obtained by assessing levels of macromolecular adducts with carcinogens or their metabolites. Development of such assays is based on examining the mechanisms of metabolic activation and detoxification of tobacco smoke carcinogens.

1. Benzo(a)pyrene. In the case of active smokers, adducts of at least 4 types of tobacco carcinogens or procarcinogens have been studied. These adducts are formed by reaction of specific metabolites of tobacco smoke constituents with DNA and/or hemoglobin. Benzo(a)pyrene (BaP), a carcinogenic representative of the polynuclear aromatic hydrocarbons in tobacco smoke is known to be metabolized to bay region diol epoxides (e.g. 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydroBaP). Such diol epoxides can bind to DNA in human tissues and lymphocytes. Antibodies developed against the major BPDE-DNA adduct have been used to assess its presence in surgical specimens of lung tissue, in human placenta, and in peripheral blood lymphocytes (89-91). Evidence for the presence of such adducts in samples from smokers has been ascertained but significant differences between smokers and nonsmokers have not been observed.

2. Aromatic Amines. 4-Aminobiphenyl and 2-naphthylamine are the known tobacco smoke constituents which are most likely to contribute to the increased risk of bladder cancer of cigarette smokers. The mechanisms by which these compounds are metabolically activated and produce DNA adducts in the bladder epithelium have been extensively studied (92). These studies have shown that the corresponding hydroxylamines are key intermediates in DNA and protein modification. The hydroxylamines also react with hemoglobin, in the case of 4-aminobiphenyl, a sulfinic acid amide of the beta-cysteine (93-95). This adduct readily releases 4-aminobiphenyl upon treatment with dilute acid. A method was developed to analyze the released 4-aminobiphenyl by gas chromatography with detection by negative ion chemical ionization mass spectrometry (95). Application of this method to smokers showed that adduct levels were higher than in nonsmokers, and decreased upon smoking cessation. The method may be further refined for assessing the uptake of carcinogenic aromatic amines from ETS by nonsmokers.

3. Ethylene. This volatile unsaturated hydrocarbon is present in both mainstream smoke (200-400 ug/cigarette) and sidestream smoke of cigarettes (96). Cigarette smoke contains also traces of the carcinogenic ethylene oxide (7.0 ug/cigarette; 97,98). Upon absorption, ethylene is metabolized to the reactive ethylene oxide. The latter binds to cellular macromolecules and to hemoglobin. The alkylated valine is cleaved off of the isolated hemoglobin and the derivatized hydroxyethylvaline is analyzed by GC-MS. Cigarette smokers showed significantly higher hydroxyethylvaline levels (389±138 pg/g hemoglobin) than nonsmokers (58±25 pg/g; 99). So far the method has not been applied to estimates of exposure of involuntary smokers to the procarcinogen ethylene.

4. Tobacco-Specific N-Nitrosamines. During tobacco processing and during smoking tobacco alkaloids give rise to tobacco-specific N-nitrosamines (TSNA). The nicotine-derived N-nitrosamines N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are powerful carcinogens. They occur in relatively high concentrations in cigarette mainstream smoke (NNN, 0.12-3.7 ug/cigarette; NNK, 0.08-0.77 ug/cigarette) and sidestream smoke (NNN, 0.15-1.7 ug/cigarette; NNK, 0.2-1.4 ug/cigarette; 40). These agents are metabolically activated by alpha-hydroxylation, leading to a highly reactive intermediate which forms DNA adducts and protein adducts (Fig. I). Metabolic activation of NNN and NNK also leads to the formation of hemoglobin adducts. Acid or base hydrolysis of these releases a keto alcohol (compound 5; Fig. I; 100). A highly sensitive GC-MS method has been developed to facilitate the detection of a derivative of compound 5. Refinement towards further increased sensitivity of the method should lead to a dosimetry assay allowing determination of the uptake of the carcinogenic TSNA by passive smokers.

FUTURE NEEDS

The absorption of tobacco-specific smoke constituents from ETS has been demonstrated through analyses of nicotine and its major metabolite, cotinine in the body fluids of exposed nonsmokers. Less tobacco-specific markers have also been measured in exposed populations; however, the results were ambiguous in regard to the quantitative uptake of ETS. There is a need to provide information about the uptake and disposition of carcinogenic constituents by individuals exposed to ETS in acute and chronic situations. Analyses to be fully developed and applied to passive smokers will include measurements of adducts of genotoxic smoke constituents covalently bound to DNA or hemoglobin. These techniques have been developed for benzo(a)pyrene, 4-aminobiphenyl, ethylene, and tobacco-specific N- nitrosamines. It is not known whether or not all of these methods can be made sufficiently sensitive to monitor the uptake of tobacco-specific components from ETS.

Nicotine in ETS is predominantly present in the vapor phase of the smoke rather than bound to the aerosol particles. In order to measure the uptake of carcinogens and toxins residing in the particulate phase of ETS, deposition studies must be developed with specific markers. Particulate phase constituents which could be quantitated include tobacco-specific N- nitrosamines, polyphenols, such as the immunoactive compound rutin, or the tobacco-specific solanesol.(101) However, the levels of these compounds are expected to be low so that development of suitable methodology calls for highly sensitive detection methods.

SUMMARY

1. The absorbtion of tobacco-specific smoke constituents from ETS has been demonstrated through analyses of nicotine and its major metabolite, cotinine in the body fluids of exposed nonsmokers.

2. The determination of nicotine or cotinine, in the saliva, serum, or urine of involuntary smokers represents a reliable, specific method for assaying the level of uptake of ETS by nonsmokers.

3. Although cotinine levels in physiological fluids of involuntary smokers generally are of the order of few percent of those of active smokers, differences in the elimination times of these compounds in active and involuntary smokers preclude a direct extrapolation to "cigarette equivalents of smoke uptake."

4. There is a further need to quantitate uptake and fate of carcinogenic constitutents of ETS-exposed nonsmokers, particularly the measurements of adducts of genotoxic smoke components attached to DNA or hemoglobin.

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Figures and Tables for Chapter 4

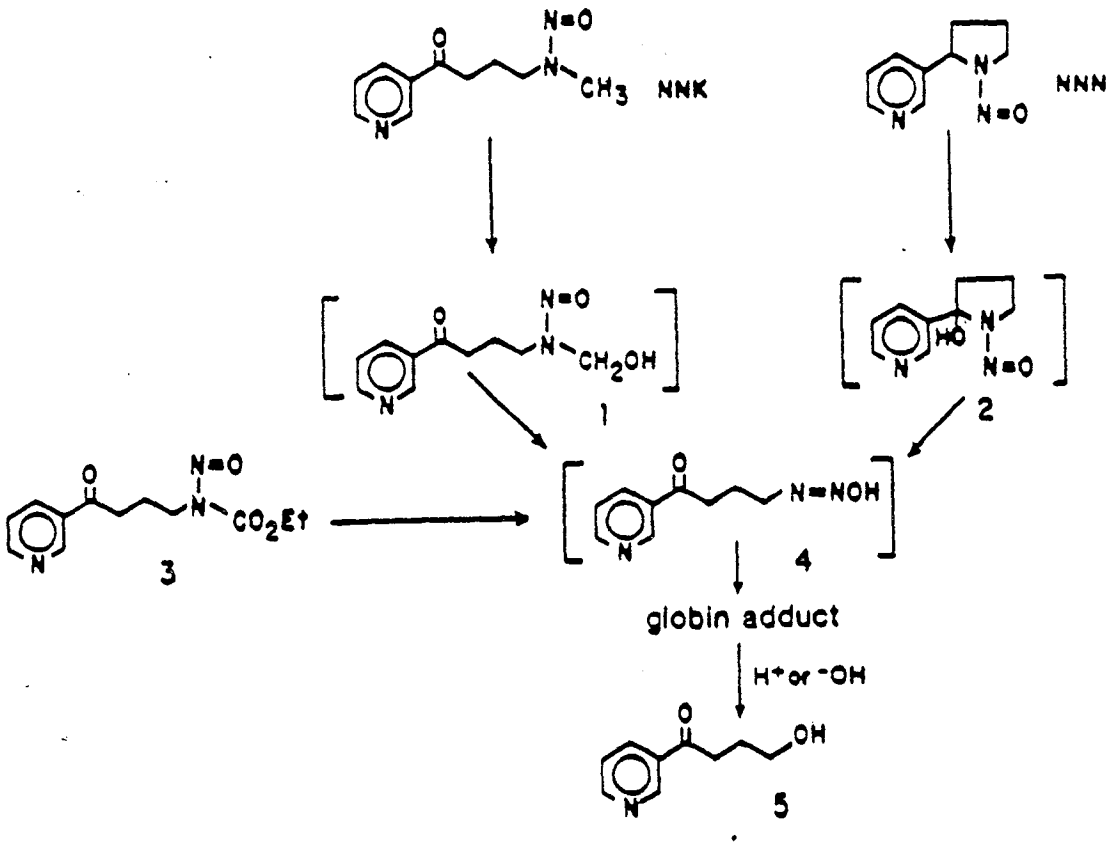

Figure I. Metabolic activation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN) to intermediates which bind to DNA and protein.

Table 4 continued ...

Nonsmoker Group	Number of Nonsmokers	Results			Reference
Children and adults	529 males 768 females	Cotinine/Saliva (ng/ml) smokers in family			Coultas et al. (53)
		none	one	≥ two	
a) <5 years old		0.0 (0.0-2.5)	3.8 (0.0-6.1)	5.4 (3.2-7.7)	
b) 6-12 years old		0.0 (0.0-2.1)	2.0 (0.0-3.8)	5.2 (1.5-7.0)	
c) 3-17 years old		0.0 (0.0-2.0)	2.9 (0.0-4.9)	4.1 (2.7-7.6)	
d) 18-29 years old		0.0 (0.0-2.6)	0.0 (0.0-5.8)	0.0 (0.0-4.4)	
e) 30-64 years old		0.0 (0.0-2.7)	1.9 (0.0-4.5)	4.4 (1.8-11.0)	
f) ≥ 65 years old		0.0 (0.0-2.6)	3.6 (0.0-6.5)	0.0	

*Numbers in parenthesis median values.

Table 4 continued ...

Nonsmoker Group	Number of Nonsmokers	Results	Reference
Municipal workers		Cotiine/Urine (ng/mg creatinine)	Sepkovic et al., (52)
I. ETS exposure in the workplace			
a) no exposure	25	4.5±0.6	
b) light expsoure	126	6.6±0.6	
c) moderate exposure	84	7.2±0.8	
d) heavy exposure	32	8.4±1.3	
II. ETS exposure in the home			
a) no exposure	77	6.1±0.8	
b) light exposure	83	6.7±0.6	
c) moderate exposure	71	7.8±1.1	
d) heavy exposure	34	7.6±1.3	
School girls (11-16 yrs) ETS exposure in the home			Jarvis et al., (53)
a) neither parent smokes	104	1.1±0.5	
b) father smokes only	76	2.0±0.6	
c) mother smokes only	40	3.2±0.8	
d) both parents smoke	110	5.0±1.0	

Continued ...

Table 4 continued ...

Nonsmoker Group	Number of Nonsmokers	Results						Reference
		Cotinine/Urine (ng/mg creatinine)						
Neonates and infants		No. exp'd	I		No. exp'd	II		Schwartz-Bicken-bach et. al., (51)
a) Mother smokes, breastfeeds	20	12	(1756)	0 -3520	8	(935)	488-2440	
b) Mother smokes, feeds bottle	16	4	(47)	0 - 160	12	(107)	0- 341	
c) Father smokes	18	10	(0)		8	(0)	0- 308	
d) No exposure in the home	15	9	(0)		6	(0)		

Table 4 continued ...

Nonsmoker Group	Number of Nonsmokers	Results				Reference
Neonates and infants		Nicotine (ng/mg creatinine)		Cotinine		Luck and
a) No exposure (4-8 days old)	10	(0)	0 - 14	(0)	0- 56	Nau, (49)
b) Exposure via breast feeding (3-8 days old)	19	(14)	5 -110	(100)	10-555	
c) Passive smoking (2.5-6 months old)	10	(35)	4.7-218	(327)	117-780	
d) Exposure via breast feeding and passive smoking (1-12 months old)	9	(12)	3.0- 42	(550)	225-870	
Infants (age 3-15 months) exposure in the home		Cotinine/ Serum (ng/ml)				Pattishall et al., (50)
Black infants						
a) no exposure	9	1.0 (1.87±2.38)				Pattishall et al., 1985
b) passive smoking	15	4.0 (5.27±3.50)				(51)
White infants						
a) no exposure	9	0.0 (0.22±0.44)				
b) passive smoking	5	0.4 (0.90±1.30)				

Table 4 continued ...

Nonsmoker Group	Number of Nonsmokers	Results		Reference
Husbands of		Cotinine/Urine (ng/ml)		Wald and Ritchie, (46)
a) nonsmokers	101	8.5± 1.3		
b) smokers	20	25.2±14.8		
Nonsmokers		Cotinine/Urine (ng/mg creatinine)		Matsukura et al., (47)
a) nonsmokers at home	200	0.5 ±0.09		
b) smokers at home	272	0.79±0.1		
Cigarettes smoked day in home of nonsmokers;		Cotinine/Urine (µg/mg) creatinine)		
1- 9	25	0.31±0.08		
10-19	57	0.42±0.1		
20-29	99	0.87±0.19		
30-39	38	1.03±0.25		
> 40	28	1.56±0.57		
unknown	25	0.56±0.16		
Infants (<10 months, not breastfed)		Nicotine/Urine (ng/mg creatinine)	Cotinine/Urine (ng/mg)	Greenberg et al.; (33)
a) not exposed to ETS	18	0 (0-59)	4 (0-125)	
b) exposed to ETS	28	53 (0-370)	351 (41-1,885)	
School children (11-16 yrs)		Cotinine/Saliva (ng/ml)		
a) Neither parent smoked	269	0.44±0.68		Jarvis et al., (48)
b) Only father smoked	96	1.31±1.21		
c) Only mother smoked	76	1.95±1.71		
d) Both parents smoked	128	3.38±2.45		

Continued ...

Table 4.

Uptake of nicotine by nonsmokers exposed to ETS under daily life conditions

Nonsmoker Group	Number of Nonsmokers	Results	Reference
		Nicotine/Urine (ng/ml)	
Hospital personnel	14	12.4±16.9	Russell and Feyerabend (29)
(78 min in smoke-filled room)	13	8.9±9.1	
Hospital personnel and outpatients		Nicotine/Saliva (ng/ml)	
a) no exposure to ETS	26	5.9 7.5	Feyerabend et al. (42)
b) exposed to ETS	30	10.1 21.6	
Flight attendants	6	Nicotine/Serum (ng/ml) pre flight: 1.6±0.8 post flight: 3.2±1.0	Foliart et al. (43)
Office workers a) 11:30 a.m. sample b) 7:45 p.m. sample after 2 hr stay in pub	7	Content/ml — Nicotine (ng) a) b) — Cotinine (ng) a) b) saliva 1.90 43.63 1.50 8.04 serum 0.76 2.49 1.07 7.33 urine 10.57 92.63 4.80 12.94	Jarvis et al. (44)
Hospital staff and outpations		Cotinine/Urine (ng/ml)	Wald et al. (45)
a) no exposure to ETS	22	2.0 (0.0 - 9.3	
b) exposed to ETS	190	6.0 (1.4 -22.0)	

Continued ...

Table 3.

Approximate Relations of Nicotine as a Parameter Between Nonsmokers, Passive Smokers, and Active Smokers[a] (41)

Nicotine/Cotinine	Nonsmokers without ETS Exposure No. = 46		Nonsmokers with ETS Exposure No. = 54		Active Smokers No. = 94
	Mean Value	% of Active Smokers' Value	Mean Value	% of Active Smokers' Value	Mean Value
Nicotine (ng/ml)					
in plasma	1.0	7	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1*	0.7	1,750
Cotinine (ng/ml)					
in plasma	0.8	0.3	2.0*	0.7	275
in saliva	0.7	0.2	2.5**	0.8	310
in urine	1.6	0.1	7.7**	0.6	1,390

[a]Differences between nonsmokers exposed to ETS compared with nonsmokers without exposure: *p<0.01; ** p<0.001.

Table 2 continued.

ETS-Conditions	No. of Passive Smokers	Results				Investigators
Room - 16 m^3	6	Time during exposure		Nicotine (ng/ml)	Cotinine (ng/ml)	Hoffmann et al., 1984 (30)
4 cigarettes concurrently and continuously smoked for 80 min; 6 air exch./hr. (200 g nicotine/m^3; 20 ppm CO)		0	Saliva	3	1.0	
			Plasma	0.2	0.9	
			Urine	17	14	
		80 min.	Saliva	730	1.4	
			Plasma	0.5	1.3	
			Urine	84	28	
		Time following exposure				
		30 min.	Saliva	148	1.7	
			Plasma	0.4	1.8	
		150 "	Saliva	17	3.1	
			Plasma	0.7	2.9	
			Urine	100	45	
		300 "	Saliva	7	3.5	
			Plasma	0.6	3.2	
			Urine	48	55	

*Nicotine and cotinine were measured in urine as ng/mg creatinine.

Table 2.

Uptake of nicotine by nonsmokers exposed to ETS under controlled conditions

ETS-Conditions	No. of Passive Smokers	Results	Investigator(s)
Room - 170 m^3 (11 smokers)		Urinary excretion	
(a) 100 cigarettes were smoked during 2 hrs; no ventilation (30 ppm CO)	7	Nicotine: 10±6.8 µg/6 hrs. Cotinine: 35±34.5 µg/6 hrs.	
(b) same conditions as above (a) but with ventilation (5 ppm CO)	7	Nicotine: 18±7 µg/6 hrs. Continine: 19±9.4 µg/6 hrs.	
Room - 66 m^3 (4 cigarette smokers)		Nicotine/Urine (µg/24 hrs)	Cano et al. (28)
(a) Day 1, nonsmoking	2	0 - 0	
" 2, 98 cig's smoked		35 - 44	
" 3, 121 " "		50 - 61	
" 4, 98 " "		62.5 - 70	
" 5, 88 " "		47 - 50	
(b) Day 1, 97 " "	2	23 - 34	
" 2, 96 " "		22.5 - 58	
" 3, 94 " "		47.5 - 69	
" 4, 103 " "		32 - 65	
Room - 43 m^3		Nicotine/Plasma (µg/ml)	Russell and Feyerabend (29)
9 smokers consumed 80 cigarettes + 2 cigars no ventilation (38 ppm CO)	12	Before exposure: 0.73±1.6 After 78 min. exposure: 0.9± 0.29 Nicotine/Urine (ng/ml) 15 min. after exposure: 80.0±58.7	

continued ...

Table 1.

Toxic and tumorigenic agents in MS and SS

Smoke Constituent	Smoke stream[a]	Cigarette A (NF)	B (F)	C (F)	D (PF)
Tar (mg)	MS	20.1	15.6	6.8	0.9
	SS	22.6	24.4	20.0	14.1
Nicotine (mg)	MS	2.04	1.50	0.81	0.15
	SS	4.62	4.14	3.54	3.16
CO (mg)	MS	13.2	13.7	9.5	1.8
	SS	28.3	36.6	33.2	26.8
Catechol (µg)	MS	41.9	71.2	26.9	9.1
	SS	58.2	89.9	69.5	117
BaP (ng)	MS	26.2	17.8	12.2	2.2
	SS	67.0	45.7	51.7	44.8
Ammonia (µg)	MS	76.0	19.4	34.0	40.4
	SS	524	893	213	236
NDMA (ng)	MS	31.1	4.3	12.1	4.1
	SS	735	597	611	685
NPYR (mg)	MS	64.5	10.2	32.7	13.2
	SS	117	139	233	234
NNN (ng)	MS	1007	488	273	66.3
	SS	857	307	185	338
NNK (ng)	MS	425	180	56.2	17.3
	SS	1444	752	430	386

[a] Abbreviations: NF, nonfilter cigarette; F, filter cigarette; PF, cigarette with perforated filter tip; BaP, benzo(a)pyrene; NDMA, N-nitrosodimethylamine; NPYR, N-nitrosopyrrolidine; NNN, N'-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

CHAPTER 5

ENVIRONMENTAL TOBACCO SMOKE AND CANCER

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Introduction

Lung cancer, an uncommon malignancy at the start of the century, has become the leading cause of cancer death in the United States (U.S. DHHS 1982). The American Cancer Society estimates that approximately 157,000 lung cancer cases will occur in the United States in 1990. Most cases are rapidly fatal and only a small proportion are cured by surgery or chemotherapy; five-year survival following diagnosis is less than 10 percent. Most lung cancers arise in the larger airways of the lung, the predominant site of deposition of inhaled particles in the size range of 0.5 to 3.0 microns in aerodynamic diameter. Primary cancer of the lung occurs in multiple histopathological patterns that are generally distinct and classifiable by conventional light microscopy. The principal types of lung cancer are squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma; in the general population, these four types account for approximately 30 percent, 20 percent, 25 percent, and 15 percent, respectively, of all lung cancers (Butler et al. 1987). Bronchioloalveolar cell carcinoma represents about 5 percent of all lung cancers. The cellular origins of the various cell types have not been established, and controversy remains concerning the specificity of associations between certain cell types and specific etiologic agents. However, in nonsmokers, adenocarcinoma is the predominant type and small cell cancers occur only rarely.

The epidemic rise of lung cancer during this century stimulated laboratory and epidemiological investigation of its causes. Most of the early epidemiological evidence indicated that tobacco smoke was a potent respiratory carcinogen, and in 1964 the Advisory Committee to the Surgeon General of the U.S. Public Health Service concluded that cigarette smoking is a cause of lung cancer (U.S. PHS 1964). The numerous investigations performed subsequently have been consistent with this conclusion. The association of lung cancer with cigarette smoking is strongest for squamous cell and small cell cancers, but the other major types are also caused by cigarette smoking. In active cigarette smokers, the risk of lung cancer increases with both the amount smoked on a daily basis and

with the duration of smoking (U.S. DHHS 1982; Doll and Peto 1978; Pathak et al. 1986). A threshold level of smoking that must be exceeded to cause lung cancer has never been demonstrated; any cigarette smoking is considered to increase lung cancer risk beyond that of the lifelong nonsmoker. In former smokers, the relative risk of lung cancer declines exponentially in comparison with those who continue to smoke.

Agents other than tobacco smoke may also cause lung cancer, and cases occur in lifelong nonsmokers. A recent study in New Mexico showed that the lifetime risks of lung cancer were 0.5 percent and 1.1 percent in female and male nonsmokers, respectively (Samet et al. 1988). Occupational exposures to arsenic, asbestos, chloromethyl ethers, chromium, coke oven fumes, nickel, and radon daughters have been linked to increased lung cancer risk, and many other occupational agents are suspect respiratory carcinogens. A family history of lung cancer is also associated with increased lung cancer risk, although a clear pattern of genetic susceptibility to lung cancer has not been demonstrated. Outdoor air pollution may contain carcinogens and indoor air may have high levels of radon, which causes cancer in exposed underground miners. Animal and human studies suggest that low consumption of vitamin A or its precursor, beta-carotene, may also increase lung cancer risk.

While studies linking active smoking to lung cancer were first published in the late 1940s and early 1950s (U.S. PHS 1964), involuntary exposure of nonsmokers to tobacco smoke was not considered as a cause of lung cancer in nonsmokers until 1981, when the first two scientific papers on this subject were published. Subsequently, many additional reports have addressed involuntary smoking as a cause of lung cancer in nonsmokers. The World Health Organization (1986), the U.S. Surgeon General (U.S. DHHS 1986), and the National Research Council (1986) have reviewed the evidence on involuntary smoking and lung cancer from human populations and judged it sufficient to support the conclusion that involuntary inhalation of tobacco smoke by nonsmokers causes cancer. This chapter reviews that evidence and the conclusions of the research organizations. The chapter also addressess the more limited evidence on involuntary smoking and cancer at sites other than the lung.

The Epidemiological Approach

Epidemiology is the scientific method used to describe the occurrence of disease in human populations and to determine the causes of disease by studying populations. Descriptive measures of disease occurrence include the incidence rate, which is the rate at which new cases of disease develop; the mortality rate, or rate of death; and the prevalence rate, which is the proportion of the population with disease. To identify the causes of disease, epidemiologists generally perform either cohort or case-control

studies. Each type of study provides an estimate of relative risk as a measure of the association between exposure and disease. The relative risk describes the comparative occurrence of disease in exposed compared with nonexposed persons.

In a cohort study, the subjects are selected on the basis of their exposure history and followed over time for the development of disease. For example, a study of involuntary smoking and lung cancer might be performed by enrolling nonsmokers married to smokers and another group of nonsmokers married to nonsmokers. The lung cancer risk associated with marriage to a smoker would be estimated by comparing incidence of or mortality from lung cancer in the two groups.

In a case-control study, cases with the disease of interest and controls without the disease are identified and their past exposures to factors of interest are assessed, often by interview. For example, a case-control study of lung cancer and involuntary smoking might be conducted by identifying nonsmokers with lung cancer and a suitable control group, and then interviewing the subjects concerning the smoking habits of their spouses, other household members, and colleagues at work.

Each type of study has advantages and disadvantages, and the results of both types may be distorted by bias. Misclassification of exposure is of particular concern in studying lung cancer and involuntary smoking. Misclassification of exposure refers to the incorrect categorization of actually exposed subjects as nonexposed and of nonexposed as exposed. When misclassification occurs randomly, it tends to bias studies towards no association, that is showing negative results; if nonrandom, it may exaggerate or reduce the apparent effect of an exposure. With regard to involuntary smoking and lung cancer, two types of misclassification are of concern. Subjects classified as nonsmokers may have actually been active smokers and the degree of exposure of nonsmokers to the smoking of others may not be accurately classified. Misclassification of both types is discussed below in relation to specific studies.

The diagnosis of lung cancer is also subject to misclassification; a cancer that originated at another primary site and then spread to the lung may be incorrectly diagnosed as a primary cancer of the lung. For example, in the case-control study reported by Garfinkel and colleagues (Garfinkel et al. 1985), 13 percent of cases originally diagnosed as lung cancer were reclassified to other sites after histological review. With regard to exposure misclassification in this study, 40 percent of the cases initially classified as nonsmokers on the basis of information in medical charts were found to be smokers on interview. Confounding refers to bias that occurs when the effect of another risk factor is mixed with the effect of the exposure of interest; thus a confounding factor is a risk factor for disease that is associated

with the exposure under investigation. For lung cancer in nonsmokers, potential confounding factors include indoor air pollution by radon and combustion products other than environmental tobacco smoke, ambient air pollution, and occupational exposures. Although confounding always merits consideration as an explanation for association, the diversity of the populations in which passive smoking and lung cancer have been associated argues strongly against confounding as the source of the association. Although individual studies may be affected by one or more biases, the totality of the epidemiological evidence as well as other relevant research are considered in judging whether an exposure adversely affects health. A bias potentially important in one study may be unimportant or adequately controlled in another. Thus review of all pertinent literature may show that bias cannot satisfactorily explain an association between exposure and disease.

Epidemiological Evidence on Involuntary Smoking and Lung Cancer

Evidence concerning involuntary smoking and lung cancer has been sought indirectly in descriptive data on mortality rates and directly with case-control and cohort studies. Time trends of lung cancer mortality across this century in nonsmokers have been examined with the rationale that temporally increasing exposure to environmental tobacco smoke should be paralleled by increasing mortality rates (Enstrom 1979; Garfinkel 1981). These data can only provide indirect evidence on the lung cancer risk associated with involuntary exposure to tobacco smoke. Enstrom (1979) calculated lung cancer mortality rates from various nationwide sources for the period 1914-1968 and concluded that a real increase had occurred among nonsmoking males after 1935. In contrast, Garfinkel (1981) found no time trends of lung cancer mortality in nonsmoking participants in two cohort studies, the Dorn Study of U.S. veterans, 1954-1969, and the American Cancer Society study, 1960-1972.

Most of the case-control and the cohort studies indicate increased lung cancer risk in nonsmokers married to smokers, but these studies do not uniformly show increased risk for sources of exposure other than smoking by the spouse (Tables 1 and 2). The first two major epidemiological studies were reported in 1981 by Hirayama and Trichopoulos and colleagues (Tables 1 and 2). Hirayama conducted a cohort study of 91,540 nonsmoking women in Japan. Mortality in these women was assessed over a 14-year follow-up period. The ratio of the observed to expected numbers of lung cancer deaths increased in a statistically significant pattern with the amount smoked by the husbands. The findings could not be explained by other factors, such as age and occupation of the husband, and were unchanged when the follow-up was extended by several years (Hirayama 1984). After its publication, the report of this study received intensive scrutiny, and correspondence in the British Medical Journal, which had published it, raised concern

about various aspects of the study's methods and findings. In his responses to the correspondence, Hirayama satisfactorily answered most of the criticisms, although he could not eliminate the possibility of unreported smoking by women classified as nonsmokers. If self-reported nonsmokers married to smokers were actually more likely to be smokers, then the resulting bias would tend to indicate an increased risk from marriage to a smoker. Based on the same population, Hirayama has also reported significantly increased risk of lung cancer for nonsmoking married men whose wives smoke (Hirayama 1984).

In 1981, Trichopoulos and coworkers (1981) also reported increased lung cancer risk in nonsmoking women married to cigarette smokers (Table 2). These investigators conducted a case-control study in Athens, Greece, that included selected histological types of lung cancer and control subjects ascertained at a hospital for orthopedic disorders. The finding of increased risk was unchanged when the case and control series were enlarged (Trichopoulos et al. 1983).

The results of subsequently reported case-control studies have also demonstrated significantly increased risk of lung cancer in nonsmokers exposed to environmental tobacco smoke (Table 2). The findings from the more recent reports based on studies throughout the world greatly strengthen the evidence from the earlier studies. Several of the newer studies included relatively large numbers of nonsmokers (Garfinkel et al. 1985; Akiba et al. 1986; Dalager et al. 1986; Lam et al. 1987; Gao et al. 1987). Furthermore, in most of the newer studies, involuntary smoking was assessed in greater detail than in the earlier reports.

The results of two other investigations have also been interpreted as showing an increased lung cancer risk associated with involuntary smoking, but both of these studies have limitations. Knoth and coworkers (1983), in Germany, described 59 lung cancer cases in females of whom 39 were nonsmokers. Based on census data, these investigators projected that a much greater than expected proportion of the nonsmokers had lived in households with smokers. In another report, Gillis et al. (1984) described the preliminary results of a cohort study of 16,171 males and females in western Scotland (Table 1); exposure to tobacco smoke in the home increased the lung cancer risk for nonsmoking men but not for nonsmoking women. This observation was based on only 16 cases of lung cancer in nonsmokers, however.

Other investigations indicate lesser or no effects of exposure to environmental tobacco smoke on lung cancer risk (Tables 1 and 2). In these studies, however, the statistical uncertainty is large because of the relatively small numbers of subjects; accordingly, the apparently negative findings are statistically compatible with the findings of those studies judged as positive. Two separate case-control studies in Hong Kong, where lung cancer

incidence rates in females are particularly high, did not indicate excess risk from involuntary smoking (Chan et al. 1979; Chan and Fung 1982; Koo et al. 1984; 1985; 1987). In the more recent of the two studies, the investigators comprehensively assessed cumulative exposure from home and workplace sources, but misclassification of exposure may have biased towards the negative results. A subsequent study in Hong Kong did find a significant association of spouse smoking and lung cancer risk (Lam et al. 1987). Lee and coworkers (Lee et al. 1986) in England reported a small case-control study with negative findings, but the statistical power of that study is limited. Another recent hospital-based case-control study, conducted in Japan, also failed to show an association between lung cancer risk and spouse smoking (Shimizu et al. 1988).

The results of the American Cancer Society's cohort study of lung cancer mortality in 176,139 nonsmoking women have also been considered by many as not showing an increased risk in those participants married to smokers (Garfinkel 1981). However, the risks for the nonsmoking women with smoking husbands were increased somewhat, but the increase was not statistically significant. Misclassification of exposure from active and involuntary smoking may have affected the results of this study. Preliminary results from a nationwide case-control study also did not demonstrate increased lung cancer risk from domestic exposure to tobacco smoke (Kabat and Wynder 1984), but the number of subjects was small. Two case-control studies of nonsmokers and smokers with selected histological types of lung cancer did not provide strong evidence for increased risk from involuntary smoking (Wu et al. 1985; Brownson et al. 1987). However, both studies included only small numbers of nonsmokers.

Conclusions on Involuntary Smoking and Lung Cancer

Scientists draw on a wide range of evidence in judging whether an agent, such as environmental tobacco smoke, causes disease. In addition to epidemiological data, the findings of laboratory studies involving in-vitro systems and of animal studies involving exposure to the agent are often relevant. Criteria have been developed for guidance in making judgments on the causality of exposure-disease relationships, but these criteria only provide guidelines, not strict rules of evidence (U.S. PHS 1964; Rothman 1986). Interpretation of the evidence on particular exposure-disease relationships often requires review by multidisciplinary panels of scientists who are instructed to reach a consensus, often in a setting of substantial uncertainty. For example, the World Health Organization regularly convenes panels of scientists to address the carcinogenicity of environmental agents.

For environmental tobacco smoke and lung cancer, the evidence has been considered by scientists convened by the International

Agency for Research on Cancer of the World Health Organization, the National Research Council, and the U.S. Surgeon General (Table 3). All three groups concluded that environmental tobacco smoke causes lung cancer among nonsmokers, although the approach used by each group was different. Consensus among the three groups, in spite of differing methodology, strengthens the determination that involuntary smoking causes lung cancer. For all three types, the biological plausibility of this association was supported by the evidence on active smoking and lung cancer, knowledge of the constituents of environmental tobacco smoke, and data demonstrating the uptake of tobacco smoke by nonsmokers.

The International Agency for Research on Cancer of the World Health Organization (1986) reviewed the evidence available through the end of 1984. It reached its conclusion concerning involuntary smoking and lung cancer largely on the basis of biological plausibility. The agency cited the characteristics of sidestream and mainstream smoke, the absorption of tobacco smoke materials during involuntary smoking, and the nature of dose-response relationships for carcinogenesis, which project some risk for any level of exposure.

In reaching its conclusion, the National Research Council committee considered the biological plausibility of an association between environmental tobacco smoke exposure and lung cancer and the supporting epidemiological evidence, available through mid-1986. The committee carefully considered the sources of bias that may have affected the epidemiological studies and concluded that the association documented in the studies could not be attributed solely to bias. Based on a pooled analysis of the epidemiological data and adjustment for bias, the report's authors concluded that the best estimate for the excess risk of lung cancer in nonsmokers married to smokers was 25%.

The 1986 report of the U.S. Surgeon General also characterized involuntary smoking as a cause of lung cancer in nonsmokers. This conclusion was based on the extensive information already available on the carcinogenicity of active smoking, on the qualitative similarities between environmental tobacco smoke and mainstream smoke, and on the epidemiologic data on involuntary smoking.

The extent of the lung cancer hazard associated with involuntary smoking in the United States has appeared uncertain. (U.S. DHHS 1986; Weiss 1986). The epidemiological studies provide varying and imprecise measures of the risk (Tables 1 and 2), and exposures to environmental tobacco smoke have not been characterized for large and representative population samples. Thus, any risk assessments for involuntary smoking and lung cancer are subject to substantial uncertainty. Nevertheless, risk assessment can provide insight into the magnitude of the lung cancer problem posed by involuntary smoking.

Repace and Lowrey (1985) used data on lung cancer mortality in Seventh Day Adventists, a nonsmoking group, to estimate the effect of exposure to environmental tobacco smoke in increasing lung cancer risk. Their analysis led to an estimate of 4,666 lung cancer deaths per year attributable to environmental tobacco smoke exposure. A later estimate gave 3,450 female lung cancer deaths and 1,440 male lung cancer deaths per year.(Repace and Lowrey, 1986) An appendix to the National Research Council's 1986 report provides estimates of the numbers of lung cancer deaths attributable to passive smoking. For the year 1985, the risk assessment projects approximately 1,000 lung cancer deaths in males and 2,000 to 3,000 lung cancer deaths in females attributable to environmental tobacco smoke. Wells (1988) attributed 3,000 lung cancer cases annually in the U.S. to involuntary smoking. A recent review of 9 published risk assessments of environmental tobacco smoke and lung cancer found they averaged about 4,500 ± 2,800 lung cancer deaths per year (Repace & Lowrey, 1990).

Further epidemiological studies of involuntary smoking and lung cancer are in progress. These studies should refine our understanding of exposure-response relationships for lung cancer and exposure to environmental tobacco smoke. Other investigations are addressing the characteristics and toxicity of environmental tobacco smoke and patterns of exposure to environmental tobacco smoke. While the results of these new studies will provide needed information for scientific purposes, the available data and the conclusions of the scientific community already provide a compelling rationale for reducing involuntary exposure to environmental tobacco smoke.

Involuntary Smoking and Cancer at Sites Other Than the Lung

Several reports have suggested that exposure to environmental tobacco smoke may increase risk of cancer at sites other than the lung. One study found that in children, maternal exposure to environmental tobacco smoke during pregnancy was associated with increased risk of brain tumors (Preston-Martin et al. 1982), and in another study paternal but not maternal smoking increased the risk of childhood rhabdomyosarcoma, a cancer of the soft tissues (Grufferman et al. 1982).

In adults, involuntary smoking has been linked to a generally increased risk of malignancy (Miller 1984). Several studies have examined excess risk at specific sites. Sandler and colleagues (Sandler, Everson, and Wilcox 1985a; 1985b; Sandler, Wilcox, and Everson 1985) conducted a case-control study on the effects of exposures to environmental tobacco smoke during childhood and adulthood on the risk of cancer. The cases included cancers of all types other than usual forms of skin cancer. For all sites combined, a statistically significant increase in risk was found for exposure to smoking by a parent (crude relative risk = 1.6) and

by a spouse (crude relative risk = 1.5); the effects of these two sources of exposure were independent (Sandler, Wilcox, and Everson 1985). Statistically significant associations were also found for some individual sites. These provocative findings will require replication in additional studies. In a case-control study, such as reported by Sandler and colleagues, biased information on exposure to environmental tobacco smoke is of particular concern. In the cohort study in Japan, Hirayama (1984) found significantly increased mortality from nasal sinus cancers and from brain tumors in nonsmoking women married to smokers. In a case-control study of bladder cancer, involuntary smoking at home and at work did not increase risk (Kabat et al. 1986). Cervical cancer, which has been linked to active smoking, was associated with duration of involuntary smoking in a case-control study in Utah (Slattery et al. 1989) This unconfirmed finding needs additional investigation.

These associations of involuntary smoking with cancer at diverse sites other than the lung cannot be readily supported with arguments for biological plausibility based on evidence from active smokers. Increased risks at some of the sites, e.g., cancer of the nasal sinus and female breast cancer, have not been found in active smokers (U.S. DHHS 1982). In fact, the International Agency for Research on Cancer (WHO 1986) has concluded that effects would not be produced in involuntary smokers that would not be produced to a larger extent in active smokers.

SUMMARY

1. For exposure to environmental tobacco smoke and lung cancer, the evidence has been considered by scientists convened by the International Agency for Research on Cancer of the World Health Organization, the National Research Council, and the U.S. Surgeon General. All three groups concluded that environmental tobacco smoke causes lung cancer among nonsmokers.

2. Further research in involuntary smoking and lung cancer will refine our understanding and are scientifically necessary; however, existing scientific conclusions already provide a compelling rationale for reducing involuntary exposure to environmental tobacco smoke.

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FIGURES AND TABLES, CHAPTER 5

TABLE 1

Cohort Studies of Involuntary Smoking and Lung Cancer

Study	Findings	Comments
91,540 nonsmoking females, 1966-1981, Japan (Hirayama 1981).	Age-occupation adjusted RR* by husbands' smoking: Nonsmokers - 1.00+ Exsmokers - 1.36 Current smokers < 20/day - 1.45 ≥ 20/day - 1.91	Trend statistically significant. All histological types of lung cancer.
176,139 nonsmoking females, 1960-1972, U.S. (Garfinkel 1981).	Age-adjusted RR by husbands' smoking: Nonsmokers - 1.00+ Current smokers < 20/day - 1.27 ≥ 20/day - 1.10	All histologies. Effect of husbands' smoking not statistically significant.
8,128 males and females, 1972-1982, Scotland (Gillis et al. 1984).	Age-adjusted RR for exposure to a tobacco smoker in the home: Males - 3.25 Females - 1.00	Preliminary, small numbers of cases.

*RR = relative risk, as estimated by the ratio of observed to expected number of lung cancer deaths.

+reference category, risk arbitrarily set to unity as the reference point for comparison.

TABLE 2

Case-control Studies of Involuntary Smoking and Lung Cancer

Study	Findings	Comments
40 nonsmoking female cases, 149 controls, 1978-1980, Greece (Trichopoulos et al. 1981).	RR* by husband smoking: Nonsmokers - 1.0 Exsmokers - 1.8 Current smokers < 20/day - 2.4 ≥ 20/day - 3.4	Trend statistically significant. Histologies other than adenocarcinoma and bronchioloalveolar carcinoma.
84 female cases and 139 controls, 1976-1977, Hong Kong (Chan et al. 1979; Chan and Fung 1982).	RR of 0.75 associated with smoking spouse, compared to 1.0 for a nonsmoking spouse.	All histologies. Two reports are inconsistent on the exposure variable.
22 female and 8 male nonsmoking cases, 133 female and 180 male controls, U.S. (Correa et al. 1983).	RR by spouse smoking: Nonsmokers - 1.00 < 40 pack years - 1.48 ≥ 41 pack years - 3.11	Significant increase for ≥ 41 pack years. Bronchioloalveolar carcinoma excluded.
19 male and 94 female nonsmoking cases, and 110 male and 270 female nonsmoking controls, Japan (Akiba et al. 1986).	For females, RR of 1.5 if husband smoked; for males, RR of 1.8 if wife smoked.	Clinical or radiological diagnosis for 43%. All types of lung cancer.
99 nonsmoking cases and 736 controls, Louisiana, Texas, New Jersey (Dalager et al 1986).	RR for marriage to a smoking spouse was 1.5	Nearly 100% histological confirmation. All types of lung cancer.
28 nonsmoking controls, New Mexico (Humble et al. 1987).	RR for marriage to a smoking spouse was 3.2 No effect in active smokers.	All types other than bronchioloalveolar carcinoma.
77 nonsmoking cases, 2 matched control series, Sweden (Pershagen et al. 1987).	RR for marriage to a smoker was 3.3 for squamous small cell carcinomas.	No effect of exposure for other types. Study based within a cohort.

TABLE 2 (continued)

Case-control Studies of Involuntary Smoking and Lung Cancer

Study	Findings	Comments
102 adenocarcinoma cases, 50 males and females, and 131 controls, Colorado (Brownson et al. 1987).	No effect in entire group. In nonsmoking women, RR of 1.7 for exposure ≥ 4 hrs/day, versus 1.0 for ≤3 hrs/day.	Involuntary smoking effect not significant in nonsmoking women, but only 19 such cases included.
25 male and 53 female nonsmoking cases with matched controls, 1971-1980, U.S. (Kabat and Wynder 1984).	RR not significantly increased for current exposure at home: Males - 1.26 Females - 0.92	All types. Findings negative for spouse smoking variable as well.
88 nonsmoking female cases, 1981-1982, Hong Kong (Koo et al., 1984, and 1985).	RR of 1.24 (not statistically significant) for combined home and workplace exposure versus 1.0 for nonexposed. No association with cumulative hours of exposure.	All types of lung cancer.
31 nonsmoking and 189 smoking female cases, U.S. (Wu et al. 1985).	No significant effects of exposure from parents, spouse, or workplace in smokers and nonsmokers.	Adenocarcinoma and squamous cell carcinoma only.
134 nonsmoking female cases, U.S. (Garfinkel et al. 1985).	Nonsignificant RR of 1.22 if husband smoked. Significantly increased RR of 2.11 if husband smoked 20 or more cigarettes daily at home. Significant trend of RR with number of cigarettes smoked at home by the husband.	All types of lung cancer. Careful exclusion of smokers from the case group.
15 male and 32 female nonsmoking cases, and 30 male and 66 female nonsmoking controls, England (Lee et al., 1986).	Overall RR for spouse smoking of 1.1.	Hospital-based study.

*RR = relative risk as estimated by the odds ratio.

TABLE 3

Conclusions of the World Health Organization, National Research Council and U.S. Surgeon General on Involuntary Smoking and Lung Cancer

World Health Organization
"Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive" smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer."
National Research Council
"The weight of evidence derived from epidemiologic studies shows an association between ETS exposure of nonsmokers and lung cancer that, taken as a whole, is unlikely to be due to chance or systematic bias. The observed estimate of increased risk is 34%, largely for spouses of smokers compared with spouses of nonsmokers."
U.S. Surgeon General
"Involuntary smoking can cause lung cancer in nonsmokers." "The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer."